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CONTENTS

Surgical Methods for Relief of Pain 373
Francis C. Grant

Effect of Vitamin E Therapy on The Central Nervous System in Amyotrophic Lateral Sclerosis 386
Charles Davison

Treatment of Prostatic Carcinoma 417
Benjamin S. Barringer

Public Health in New York City 423
Charles F. Bolduan

Library Notes:

Recent Accessions to the Library 441

Proceedings of Academy Meetings 442

Committee on Medicine and The Changing Order . . 446

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JUNE, 1943

SURGICAL METHODS FOR RELIEF OF PAIN*

FRANCIS C. GRANT

Professor of Neurosurgery, University of Pennsylvania School of Medicine

PAIN and its relief is a chief cause for the development of medicine. Drugs, opium and alcohol, were the first reliance of the physician. Gradually, as knowledge increased of the sensory pathways along peripheral nerves and in the central nervous system, surgeons were called upon to relieve pain by section of these fibers. But surgical section of pain pathways has disadvantages. Most peripheral nerves carry both sensory and motor fibers; their severance causes motor paralysis as well as anesthesia. Section of the posterior roots of the spinal cord produces a complete loss of all modalities of sensation, touch, pain and most important, muscle sense. If the posterior roots leading to an extremity are sectioned, the resulting loss of sense of position produces a disability as crippling as that which follows motor paralysis. But this particular disadvantage was overcome by the careful clinical observation of Spiller[1] who showed that the antero-lateral columns in the spinal cord carried only pain and temperature fibers. If this tract is sectioned the contralateral half of the body is rendered analgesic without the loss of function consequent upon interference with touch and muscle sense. The

* Read October 19, 1942 at the fifteenth Graduate Fortnight of The New York Academy of Medicine.

incision into the cord is made with greatest safety and operative convenience at the level of the first thoracic segment. By this procedure pain referred to any area below the level of the ensiform cartilage can be relieved. Pain in the face is abolished by section of the sensory root of the trigeminal; pain in the tonsil and throat by severance of the trigeminal and glossopharyngeal nerves; pain in the neck and shoulders responds well to rhizotomy of the upper four or five cervical posterior roots, since the function of position sense in the muscles in the areas supplied by these nerves is relatively of little importance. But pain referred to the axilla, upper arm, forearm, and fingers is still a problem. Brachial plexus section or rhizotomy of the lower cervical and top thoracic posterior roots produces practical paralysis of the corresponding arm due to complete loss of muscle sense, and, incidentally, is not very effective in checking the pain. High cervical cordotomy at the level of the second cervical segment can be performed. but the neurosurgeon should keep in mind the possibility of phrenic paralysis. Recently section of the major pain pathways in the medulla and in the internal capsule have been suggested and successfully carried out to produce complete hemianalgesia. That such hitherto inaccessible sensory pathways should have been singled out for attack is evidence that the problem of unbearable pain cries out for solution.

In the clinic with which I am connected much contact has been had with pain since Drs. Spiller and Frazier[2] between them worked out the technique for preganglionic section of the sensory root of the trigeminal and for section of the antero-lateral columns of the spinal cord. Trigeminal neuralgia was our first problem. This has been solved by cutting the outer four-fifths of the sensory root preferably through the temporal fossa. We speak of the solution of this problem, but it has not really been solved. Root section will relieve the paroxysmal and devastating pain in the face. Nevertheless about 5 per cent of these patients develop a burning paresthesia in the anesthetic area of the face and are even more miserable following operation than before since the burning pain is persistent. For this reason we were greatly interested in Sjökvist's report on section of the descending root of the trigeminal in the medulla. He claimed that section of this descending root would sever only pain fibers, leaves touch sensation undisturbed and thus spares the patient the subjective sensation of sensory loss. Weinberger[3] in this clinic modified the Sjökvist[4] technique in such a way as to avoid injury

to the restiform body and thus reduce postoperative neurologic sequellae to a minimum. By this procedure pain in the face can be abolished with but the slightest objective and no subjective loss of touch sensation.

But medullary tractotomy is not a suitable procedure for routine use. Sufferers from major trigeminal neuralgia are elderly, many hypertensive and feeble. Medullary tractotomy requires a general anesthesia given in the prone position. Local anesthesia cannot be used since medullary section is painful and a sudden movement of the patient at the time of this incision might result in disaster. The cerebellar tonsil and posterior inferior cerebellar artery require retraction. The landmarks for the medullary incision are not of the best. That part of the descending root carrying fibers to the third division lies most centrally in the medulla. The mandibular area is commonly involved in trigeminal pain. Therefore, to be certain to section these fibers the medulla must always be deeply incised. Ten cases of true trigeminal neuralgia have been operated by this technique without mortality or permanent neurologic sequellae but with complete relief of pain in only eight. Since trigeminal neuralgia is not a lethal disease, any operative procedure used in its relief must be the simplest and safest available. By the subtemporal approach the mortality does not exceed 1.8 per cent. The potentialities for disaster in any suboccipital approach are much greater than in the subtemporal. Medullary tractotomy has, therefore, been abandoned as a routine procedure in the relief of major trigeminal neuralgia.

Although a number of leading neurosurgeons are not of this opinion, we have for a long time appreciated the value of alcohol injection as an initial step in the treatment of trigeminal neuralgia. It is of importance in differential diagnosis. Furthermore, an alcohol injection accustoms the patient to the sensation of complete anesthesia in the face. When after a year or longer his anesthesia disappears and his pain returns, he is entirely cognizant of how his face will feel after his root has been cut. He accepts his permanent anesthesia much more readily if he knows by experience just what abnormal sensations he must expect in return for complete relief of pain. Seventy-eight per cent of the cases in our records complaining bitterly of postoperative paresthesias were subjected to root section as a primary procedure without preliminary preparation by alcohol injection. Nerve block is painful and not consistently successful. But, nevertheless, it should always be attempted before per-

TABLE 1

CANCER OF MAXILLARY ANTRUM AND UPPER JAW

Cases	
Pain relieved	38
Pain partially relieved	9
Pain not relieved	8
Died	3
Total	58

TREATMENT		RESULTS	NO. OF CASES
	2nd Division	Pain relieved	15
		Pain not relieved	6
Alcohol injection	3rd Division	Pain relieved	3
		Pain not relieved	2
	2nd and 3rd Divisions	Pain relieved	7
		Pain 60% relieved	6
Intracranial neurectomy, 2nd and 3rd Divisions		Pain relieved	5
		Pain 75% relieved	3
		Died	1
Avulsion of sensory root		Pain relieved	8
		Died	2

manent anesthesia is produced by root section.

Cancer is only too frequently accompanied by intractable pain. Should reliance be placed on morphine and its derivatives to allay suffering, or should an attempt be made to relieve the pain by blocking afferent pathways leading from the involved area? The pain from cancer is constant and harrowing, without surcease by night or day. Relief afforded by morphine is intermittent; pain ceases when the drug takes hold, then reappears. The patient bears with it as long as he can, then begs for more morphine. But section of afferent pathways, carefully planned and properly performed, can result in complete and permanent relief of pain.

Unfortunately, however, the problem is not as simple as it seems. The methods at one's disposal for the relief of pain are not completely satisfactory. Cordotomy, rhizotomy, section of the branches or the sensory root of the trigeminal nerve, or injection of alcohol into the spinal

TABLE II

CANCER OF ETHMOID AND SPHENOID SINUSES: CHEEK AND SKIN

Ethmoid and Sphenoid Sinuses	*Cases*
Pain relieved	2
Pain partially relieved	2
Pain not relieved	3
Total	7

TREATMENT		RESULTS	NO. OF CASES
Alcohol injection	2nd Division 5th cranial nerve	Pain relieved	1
		Pain not relieved	3
Avulsion of sensory root Fifth nerve		Pain relieved	1
		Pain 60% relieved	1
		Pain not relieved	1
	Cheek, skin		24
		Pain relieved 19	
		Pain not relieved 3	
		Died 2	
Alcohol injection	2nd Division	Pain relieved	7
		Pain not relieved	2
	2nd and 3rd Division	Pain relieved	4
		Pain not relieved	1
Intracranical neurectomy 2nd and 3rd Divisions		Pain relieved	4
Avulsion of sensory root 5th nerve		Pain relieved	4
		Died	2

subarachnoid space all involve the patient in definite hazards. Cordotomy, rhizotomy, or section of the trigeminal root imply a major surgical operation with its attendant risks in persons already debilitated by malignant disease. The antero-lateral columns lie adjacent to the pyramidal tracts. A badly placed incision in the cord can result in motor weakness in the extremities. Furthermore, bilateral cordotomy is followed in at least 10 per cent of cases by urinary retention, temporary or permanent. Rhizotomy causes complete loss of all modalities of sensation. If it is performed for pain in the arm due to involvement of the brachial plexus consequent on metastasis from mammary cancer, the arm and hand are rendered useless, for, although they can be moved, no

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TABLE II

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Ethmoid and Sphenoid Sinuses	*Cases*
Pain relieved	2
Pain partially relieved	2
Pain not relieved	3
Total	7

TREATMENT		RESULTS	NO. OF CASES
Alcohol injection	2nd Division 5th cranial nerve	Pain relieved	1
		Pain not relieved	3
Avulsion of sensory root Fifth nerve		Pain relieved	1
		Pain 60% relieved	1
		Pain not relieved	1
	Cheek, skin		24
		Pain relieved 19	
		Pain not relieved 3	
		Died 2	
Alcohol injection	2nd Division	Pain relieved	7
		Pain not relieved	2
	2nd and 3rd Division	Pain relieved	4
		Pain not relieved	1
Intracranical neurectomy 2nd and 3rd Divisions		Pain relieved	4
Avulsion of sensory root 5th nerve		Pain relieved	4
		Died	2

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TABLE III

CANCER OF MANDIBLE

	Cases
Pain relieved	25
Pain not relieved	9
Died	3
Total	37

TREATMENT		RESULTS	NO. OF CASES
Alcohol Injection	3rd Division	Pain relieved	11
		Pain not relieved	6
	Inferior dental and lingual nerves	Pain not relieved	1
	2nd and 3rd Divisions	Pain relieved	6
		Pain not relieved	2
Avulsion of sensory root		Pain relieved	8
		Died	3

sense of their position remains. Subarachnoid injection of alcohol may paralyze motor as well as sensory nerves and cause urinary retention or weakness in the lower extremities.

The problem of relief of pain is further complicated by the spread of the cancer with the involvement of afferent pathways adjacent to those severed. A uterine or prostatic cancer may cause intense pain in one flank or down one leg. A unilateral cordotomy or subarachnoid alcohol block may give relief for two or three months. Then, as the growth spreads, equally severe distress may appear on the opposite side.

From the practical standpoint, therefore, the decision to attempt to relieve pain by blocking afferent pathways must rest on a number of factors: the position and rapidity of growth of the cancer; the probable period of life expectancy of the patient; the amount and location of the pain; the patient's reaction to it, and the dosage of opium necessary for its control. Finally, the patient's general condition as an operative risk requires careful consideration before radical surgical intervention is proposed. Roentgenograms of the chest should always be taken to determine the presence or absence of pulmonary metastases. If the lungs

TABLE IV

CANCER OF CHEEK, MUCOUS MEMBRANE AND TONGUE

Cheek, Mucous Membrane	*Cases*
Pain relieved	7
Pain partially relieved	3
Pain not relieved	2
Total	12

TREATMENT		RESULTS	NO. OF CASES
Alcohol injection	2nd Division	Pain relieved	7
		Pain 50% relieved	3
		Pain not relieved	2
	Tongue		21
		Pain relieved 12	
		Pain partially relieved 6	
		Pain not relieved 3	
Treatment			
Alcohol injection	3rd Division	Pain relieved	9
		Pain partially relieved	4
		Pain not relieved	2
	Inferior dental and lingual nerves	Pain partially relieved	2
	2nd and 3rd Divisions	Pain relieved	3
		Pain not relieved	1

are involved, or if the sufferer's general physical condition suggests a life expectancy of less than three months, radical surgical intervention should not be attempted unless the pain is devastating. Under such conditions an attempt to block afferent pathways by the injection of alcohol into the subarachnoid space or further recourse to morphine is indicated.

Our purpose is to show what can be done for relief of pain by interruption of sensory pathways, the hazards involved, and what justification exists for suggesting these procedures rather than continuing with morphine or dilaudid hydrochloride sedation. Three groups of patients have been selected: those with pain in the face, jaw, mouth and sinuses with or without metastases to the cervical glands; those with pain in the arm from mammary cancer or axillary or supraclavicular metastases

TABLE V

CANCER OF BASE OF TONGUE, TONSIL AND NECK

Base of Tongue and Tonsil	*Cases*
Pain relieved	21
Pain partially relieved	9
Pain not relieved	17
Died	3
Total	50
Neck	
Pain relieved	7
Pain partially relieved	2
Total	9

TREATMENT	RESULTS	NO. OF CASES
Alcohol injection 3rd Division	Pain not relieved	15
	Pain partially relieved	8
Avulsion of sensory root	Pain relieved	8
	Pain partially relieved	1
	Pain not relieved	2
	Died	1
Avulsion of 5th and 9th nerves	Pain relieved	13
	Died	2
Cervical rhizotomy; posterior cervical roots of 1st to 5th cranial nerves	Pain relieved	7
	Pain partially relieved	2

involving the brachial plexus; and lastly a group with abdominal or pelvic disease producing pain anywhere below the ensiform process.

In the first group the afferent pathways involved comprise the trigeminal and glossopharyngeal nerves and the upper four or five cervical posterior roots. Cancer about the face is a common and, at times, distressingly painful condition. The simplest problem to handle is those cancers lying within the sensory distribution of the trigeminal. Alcohol block of the appropriate branch should always first be attempted. But, that the malignancy, especially when it involves the maxillary antrum, ethmoid or sphenoid, may displace the second division from its usual anatomic position, thus making accurate injection difficult or impossible, must be kept in mind. Those cancers lying within the sensory field of the second division are most effectively relieved, because a block of all three divisions by root section gives a wide area of anesthesia about the growth into which the malignancy can spread without producing more

TABLE VI

ANALYSIS OF RESULTS AFTER CORDOTOMY FOR RELIEF OF PAIN

	Cordotomies	
126 patients (58 women, 68 men)	131	
Bilateral cordotomy	56	
Unilateral cordotomy	70	
	Number	*Per Cent*
Completely relieved	80	64
75% relieved (8 recurrences opposite side)	19	15
50% relieved (6 recurrences opposite side)	9	7
Not relieved	5	4
Died	13	10

pain. When the pain is referred to the tongue or floor of the mouth, a third division block is indicated. If it is not completely successful, the superficial cervical roots may be dissected out and sectioned where they swing forward over the sternocleidomastoid muscle. If an alcohol block is unsuccessful, sensory root section or preganglionic section of the second and third divisions can be carried out by the subtemporal approach, a simple procedure readily performed under local anesthesia alone. Pain in the base of the tongue, tonsil or throat indicates ninth nerve involvement. The easiest way to section the glossopharyngeal is by a unilateral suboccipital craniectomy. A short extension downward permits exposure of the upper three cervical roots. With the medulla thus widely exposed, a tractotomy on the descending root of the trigeminal is to be preferred to root section at the pons. In our experience tractotomy is easier and just as satisfactory in producing relief as root section. This is the most effective use for tractotomy, and its value has been repeatedly proven. The only referred pain above the clavicles which cannot be relieved by one or more of these maneuvers is that deep in the ear. Fortunately such pain is uncommon. Three patients with cancer of the tonsillar pillars had such complaint. In one patient the fifth, seventh, eighth, ninth and twelfth nerves together with the upper three cervical posterior roots were sectioned without the slightest relief of this pain.

When a mammary cancer or a pulmonary sulcus tumor spreads to

TABLE VII

SUMMARY OF TYPES OF PAINFUL LESIONS REQUIRING CORDOTOMY

	No. of Cases
Cancer of urogenital tract or genitalia	74
Cancer of vertebrae	26
Gunshot wounds of spine	4
Retroperitoneal sarcoma	2
Other causes	20

invade the brachial plexus, intense pain in the shoulder, arm, forearm or hand results. The answer to this problem might seem easy, section of the posterior roots from the third cervical to the first thoracic segments. This can be done, but the arm and hand are useless since all modalities of sensation are lost. Furthermore, the useless insensitive arm is heavy and drags on the shoulder, causing added discomfort. Rhizotomy is not a satisfactory answer to this problem in most cases. The alternatives are high cervical cordotomy, section of the pain fibers in the medulla, or in the cerebral crus. Four high cervical cordotomies at the level of the second or third cervical segment have been carried out, two combined with posterior root section from the fourth to the seventh cervical segments. One cordotomy and one combined cordotomy and root section were successful, the other two failed to relieve the pain effectively. If the eighth cervical and first thoracic posterior roots are spared, enough sense of position remains in the fingers to allow some use of the hand and fingers. A cordotomy at the second cervical segment should eliminate all pain below the fifth or sixth cervical distribution. But cordotomy plus rhizotomy is a more extensive and therefore more dangerous procedure than a simple cordotomy. We have had no experience with section of the pain fibers in the medulla as described by Schwartz and O'Leary[5] and J. C. White.[6] In a single case the sensory pathways were cut in the crus with fortunately complete relief of pain, although the subsequent sensory examinations showed that we had not followed Walker's[7] technique with accuracy.

Pain referred to any area below the ensiform cartilage can be re-

TABLE VIII

COMPLICATIONS AFTER BILATERAL CORDOTOMY

	No. of Cases
Vomiting	15
Distention	17
Retention of urine (Eight patients had cancer of bladder, four had previous subarachnoid alcohol injection)	26
Motor weakness	10
Died	8
Meningitis 2	
Shock 2	
Cachexia 4	

lieved by cordotomy at or just above the level of the first thoracic segment. It is important to cut the antero-lateral tracts at this level because it is above the point at which the sympathetic fibers enter the cord. If any doubt exists as to the proper level for section, a carefully induced spinal anesthesia with accurate observation as to the level to which the anesthesia must be carried to produce relief of pain is valuable. This test is especially important when an attempt is to be made to relieve the pain of tabetic crises. Cordotomy, whether uni- or bilateral, can be carried out under local anesthesia, since section of the antero-lateral tracts is not in itself painful. Local anesthesia permits of testing of the level of analgesia as the tracts are incised. Once an adequate level to include the area to which the pain is referred has been reached, no further incision into the cord is necessary. In this way any damage to adjacent pyramidal tracts can be avoided. A bilateral section should be done in the same way, but the two incisions should never be made at the same level. Usually one incision is made at cervical eight or thoracic one, and the opposite tract cut at thoracic three or four. If both columns are cut in the same segment, a complete transverse myelitis may result. The dangers accompanying cordotomy are involvement of the lateral pyramidal tracts with consequent motor weakness or of the anterior pyramidal pathways resulting in sphincteric disturbances.

Why cordotomy, why not inject alcohol into the subarachnoid

TABLE IX

COMPLICATIONS AFTER UNILATERAL CORDOTOMY

	No. of Cases
Vomiting	5
Distention	5
Retention of urine (Three had cancer of prostate. Three had previous subarachnoid alcohol injection)	8
Motor weakness (Two had previous subarachnoid alcohol injection)	6
Died	5
Cachexia 3	
Pneumonia 2	

TABLE X

RESULTS WITH INJECTION OF ALCOHOL INTO THE SUBARACHNOID SPACE

	Number of Patients	Per Cent
Total patients	31	
Relief of pain	15	50
Partial relief of pain	6	20
No relief of pain	10	30
Hemiparesis after injection	1	
Paralysis of legs and sphincters after injection	1	

space as suggested by Dogliotti?[8] A number of alcohol injections have been done. The results have been satisfactory, considering the easy technique demanded by this procedure. No question exists but that this is an effective means for relieving pain. But we are not impressed with this procedure. Many patients have been seen in whom alcohol was injected in other clinics and who have come for further relief. The chief objection to alcohol is that its effect is uncertain and uncontrolled. Furthermore, if alcohol is ineffective in relieving pain it may still destroy

the fibers to the sphincters on one side. If now a unilateral cordotomy is necessary, the pathways governing sphincter control on the opposite side are implicated and retention may result. Loss of sphincter control should never follow a unilateral cordotomy unless the bladder is already involved by the malignancy. In our opinion a unilateral cordotomy carried out through a hemilaminectomy under local anesthesia is almost as safe and much more likely to result in complete relief of pain, and is accompanied by less chance of untoward complications than is the injection of alcohol into the lumbar subarachnoid space.

Severe pain in many areas of the body can be relieved, at a price. The pain of trigeminal neuralgia at the price of anesthesia of the face and the remote chance of a persistent paresthesia in the anesthetic zone. The pain of cancer can be relieved—at a price, the price of an operative procedure, loss of sensation, possible motor weakness and sphincteric disturbance. The question becomes, therefore, one of expediency. Is the pain sufficiently severe to advise the patient that the price he may have to pay for relief is not too high? If our experiences with this problem have helped to answer this question, this paper has served its purpose.

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EFFECT OF VITAMIN E THERAPY ON THE CENTRAL NERVOUS SYSTEM IN AMYOTROPHIC LATERAL SCLEROSIS*

CHARLES DAVISON

Neuropathologist, The Montefiore Hospital

UNTIL recently it was universally recognized that amyotrophic lateral sclerosis is not amenable to any form of treatment. Wechsler,[1] on the basis of experimental studies of animals that were deprived of Vitamin E and which developed paralysis and atrophies (Ringsted,[2] Lipshutz,[3] Burr, Brown and Moseley,[4] Einarson and Ringsted[5]), believed that patients suffering from amyotrophic lateral sclerosis might respond to a synthetic preparation containing alpha tocopherol. Wechsler,[1] Rosenberger,[6] and Bicknell[7] found that alpha tocopherol and natural Vitamin E act favorably in some cases of amyotrophic lateral sclerosis and bring about varying degrees of improvement, perhaps in inverse ratio to the age and duration of the disease. Doyle and Merritt,[8] Denker and Scheinman[9] and Ferrebee, Klingman and Frantz,[10] however, using the same form of treatment were unable to produce improvement or to arrest the course of the illness in patients with amyotrophic lateral sclerosis.

A number of cases of amyotrophic lateral sclerosis were treated at the Montefiore Hospital with Vitamin E and alpha tocopherol. Ten of these cases came to necropsy and except for one, none responded clinically to this form of treatment. The age, duration of the illness, and the fact that they may not have been treated adequately may be used as arguments against the lack of improvement. In this presentation, emphasis will be placed on the possible influence of this form of treatment on the affected structures of the central nervous system and not on the clinical results. The ten cases of amyotrophic lateral sclerosis that received Vitamin E were investigated histopathologically and compared with material from about forty untreated cases. As will be demon-

* From the Neuropathological Laboratory and the Neuropsychiatric Division of the Montefiore Hospital for Chronic Diseases, New York. Read at the Combined Meeting of the New York Neurological Society and the Section of Neurology and Psychiatry on October 6, 1942 at The New York Academy of Medicine.

strated, in many of the treated cases, the destruction of myelin sheaths and axis cylinders was less intense than in the untreated cases, while the dense gliosis which is usually present in amyotrophic lateral sclerosis, was diminished or almost absent in those that received Vitamin E. The anterior horn cells and the nerve cells of the involved bulbar nuclei remained unchanged and showed no signs of reversibility.

Methods of Procedure

Ten cases (Tables I and II) of amyotrophic lateral sclerosis that received Vitamin E in the form of ephynal, alpha tocopherol, a diet rich in Vitamin E, thiamine chloride, wholewheat germ oil and bile salts form the basis of this presentation. Two patients received ephynal by mouth without intramuscular injections of alpha tocopherol. The treatment in the other eight cases conformed to that outlined by Wechsler.[1]

Sections from various cortical areas (where available), internal capsule, peduncles, pons, medulla oblongata and spinal cord were embedded in parlodion and stained by the myelin sheath and cresyl violet methods. Frozen sections were stained by the myelin sheath, Bielschowsky, Sudan III and Holzer methods. For purposes of comparison the gliosis in the untreated cases was designated as dense while in the treated cases there were gradations which were divided into moderate, slight or very slight gliosis. Brief clinical and histopathological reports pertaining only to the specific problem will be given.

Report of Cases

I. Cases Treated with Vitamin E Including Alpha Tocopherol Intramuscularly, Showing Significant Changes in the Involved Pathways.

Case 1—F.E., a man, aged 64, was admitted to this hospital on December 16, 1939 with a history of difficulty in pronouncing consonants since February 1939 followed later by choking episodes while swallowing, regurgitation of food through the nose, dyspnea on exertion and spontaneous laughing and crying. The speech became more indistinct. Later, there appeared fibrillations of muscles of the arms and legs, sialorrhea and progressive weakness of the upper and lower extremities.

Neurological examination disclosed: atrophy, moderate weakness and fibrillations of the muscles of the shoulder, arm and hand; hyper-

TABLE I

CASES TREATED WITH VITAMIN E INCLUDING ALPHA TOCOPHEROL INTRAMUSCULARLY SHOWING SIGNIFICANT CHANGES IN THE INVOLVED PATHWAYS

Patient	*Sex*	*Age*	*Duration of Illness*	*Treatment with alpha tocopherol*	*Histologic Picture*
1	M	64	1 yr., 10 mo.	7½ months.	Myelin sheath—No demyelinization noted. H.P.—Slight changes—insular. Bielschowsky—slight changes. Fat—None. Holzer—very faint gliosis—insular.
2	M	60	2 yrs., 7 mo.	1 month and 4 days.	M.S.—faint demyelinization with small islands of myelin sheath swelling and destruction. Axis cylinders slightly less than in ordinary cases. Holzer—faint gliosis.
3	M	44	6 yrs.	4 months and 5 days. Treated intensively.	M.S.—hardly any pallor. H.P.—slight disintegration of fibers—insular. Bielschowsky — slight disintegration. Fat—present—not as much as in ordinary cases. Holzer—slight gliosis—insular.
4	F	53	1½ yrs.	7 months and 3 weeks.	M.S.—no visible demyelinization. H.P.—slight disintegration of fibers—insular. Bielschowsky — silght disintegration. Fat—none. Holzer—faint gliosis—insular.
5	F	70	1 yr., 1 mo.	2 months and 7 days.	M.S.—very slight demyelinization. H.P.—slight changes—insular Fat—very little. Bielschowsky—slight changes. Holzer—faint gliosis—insular.
6	M	54	2 yrs.	5 weeks and 3 days. Received treatment also on the outside, but could not determine exact amount. This patient showed slight improvement in neurological symptoms.	M.S.—slight pallor of left and slight demyelinization of right crossed pyramidal tracts. H.P.—destruction, however, not as marked as in average case; more marked on the right. Fat—same as in ordinary cases. Bielschowsky—destruction, but less than in ordinary cases, especially on the right. Holzer—moderate gliosis in right crossed pyramidal and very slight on the left.

TABLE II

CASES TREATED WITH VITAMIN E, SOME INADEQUATELY, WITHOUT SIGNIFICANT CHANGES IN THE INVOLVED PATHWAYS

Patient	*Sex*	*Age*	*Duration of Illness*	*Treatment with alpha tocopherol*	*Histologic Picture*
7	M	53	1 yr., 11 mo.	15 days.	M.S.—A.C., glia and deposition of fat not much different from ordinary cases of amyotrophic lateral sclerosis.
8	M	50	2½ yrs.	3 mo., 10 days.	M.S.—moderate destruction. A.C.—moderate destruction. Fat—some fat droplets but not as much as in usual cases. Holzer—moderate gliosis.
9	F	49	2 yrs.	1 yr. — Fairly intensive treatment but with interruptions.	M.S.—demyelinization and disintegration of myelin sheaths. Fat—same as average. Weichowsky—about same as average case. Holzer—moderate gliosis—slightly less than average.
10	F	62	2½ yrs.	7 months with some interruptions.	This case did not differ neuropathologically from untreated cases of amyotrophic lateral sclerosis.

active deep reflexes but no Babinski or allied signs; diminished abdominals and cremasterics; a motor 5th and supranuclear 7th paresis on the right; paresis of the soft palate; adductor paresis of the right vocal cord; impaired swallowing; paresis of the left trapezius and sternomastoid muscles; fibrillation of the muscles of the tongue and forced laughing and crying.

Laboratory Data: negative.

Course: The patient remained ambulatory and active. He received alpha tocopherol and the other ingredients from February 7, 1940 until September 27, 1940. He developed pneumonia and expired on December 17, 1940.

Autopsy Report – Microscopic examination – The various *cortical areas, internal capsule, peduncles* and the *pyramids in the pons* and *medulla oblongata* disclosed no abnormalities. There were no areas of demyelinization or alteration in the myelin sheaths and axis cylinders

in the pyramidal pathways. The nerve cells of the 10th and 12th nerve nuclei were diminished in number and showed shrinkage, pyknosis, chromatolysis or complete disintegration

Spinal cord: Areas of demyelinization could not be detected with very low power in the myelin sheath preparation (Fig. 1A). With higher magnification, however, there were islands of slight alteration in the size and breaking-down of some of the myelin sheaths in the crossed pyramidal tracts (Fig. 2A). Swelling of a few myelin sheaths could also be detected in parts of the pyramidal tracts that appeared uninvolved (Fig. 2C). In the Bielschowsky preparation, the axis cylinders of the above fibers showed swelling, fragmentation and bulbous terminations within the region of the crossed pyramidal tracts (Fig. 3A). The other axis cylinders within this tract except for swelling did not disclose marked pathological changes. In the Sudan III preparation, fat could hardly be detected in any of the pathways (Fig. 4A). An occasional droplet was seen. In the Holzer preparation, gliosis could not be seen in the pyramidal tracts with lower magnification (Fig. 5A). With higher magnification, however, small perivascular areas of gliosis could be detected (Fig. 6A). In the cresyl violet preparation, there was diminution in the number of anterior horn cells which showed all types of pathological changes such as loss of chromatin, disintegration, shrinkage and slight pyknosis.

Comment: This patient received large doses of Vitamin E and B for a period of seven and one-half months without any noticeable clinical improvement. Histopathologically, there was hardly any demyelinization of the pyramidal tracts and the little that was present was seen only in the spinal cord. Small islands of myelin sheaths and axis cylinders, however, were found destroyed. In the Holzer preparation, there was hardly any gliosis; the little that was present consisted of a few islets of glial fibers. No fatty deposits could be demonstrated in the pyramidal pathways of the spinal cord. This patient also had a supranuclear 5th and 7th which would indicate a lesion of the aberrant pyramidal tract fibers. Degeneration of such fibers could not be demonstrated and it is possible that the Vitamin E may have helped towards the removal of the products of disintegration.

CASE 2—V.G., a man, aged 60, was admitted to this hospital on April 22, 1940 with a history of twitching of the muscles of the neck, forearms and hands since January 1938. One year later, the patient became

Fig. 1A

Fig. 1B

Fig. 1A (Case 1)—Lack of visible demyelinization in the pyramidal pathways of a case of amyotrophic lateral sclerosis treated with Vitamin E. Compare with *Fig. 1B* from a non-treated case showing extensive demyelinization of the crossed pyramidal and left direct pyramidal tracts. Myelin sheath stain.

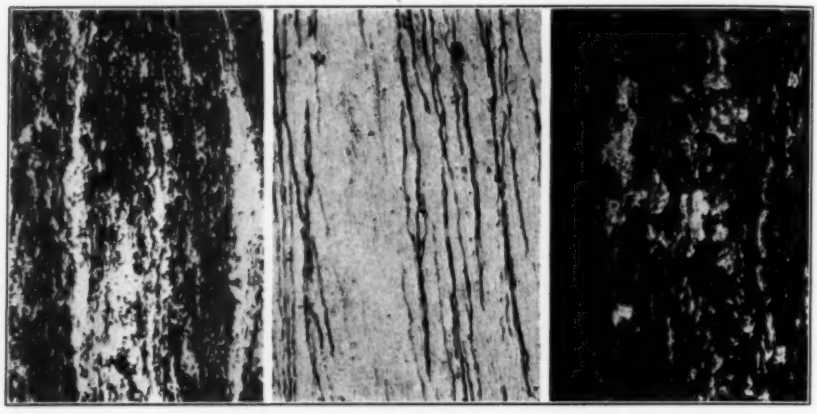

Fig. 2A Fig. 2B Fig. 2C

Fig. 2A (Case 1)—Insular myelin sheath destruction from a case treated with Vitamin E. Compare with *Fig. 2B* of extensive myelin sheath destruction from an untreated case. Myelin sheath x 240. *Fig. 2C* (Case 1)—Slight disintegration and swelling of single myelin fibers in parts of the pyramidal tracts that appeared uninvolved from a case of amyotrophic lateral sclerosis that received Vitamin E. Myelin sheath x 480.

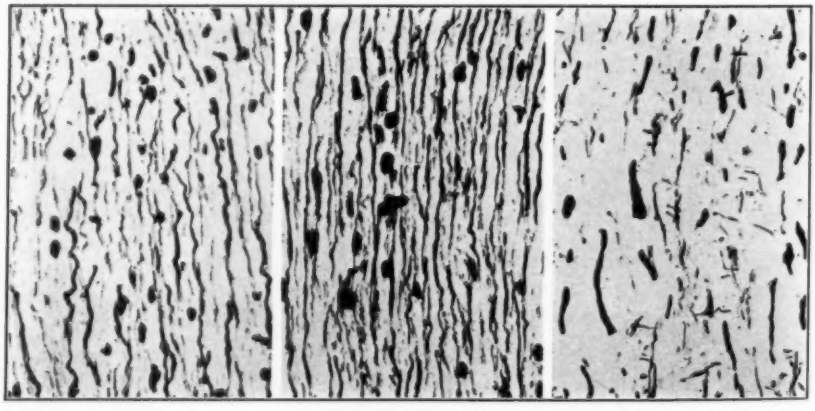

Fig. 3A Fig. 3B Fig. 3C

Fig. 3 (Case 1)—*A:* Axis cylinders from the crossed pyramidal tract of a case of amyotrophic lateral sclerosis treated with Vitamin E. Compare with *B* from a normal case and *C* an untreated case of amyotrophic lateral sclerosis. In *A* there is slight diminution in number, swelling and slight tortuosity of axis cylinders when compared with the normal *B* and the severely diseased, fragmented and swollen axis cylinders of the untreated case of amyotrophic lateral sclerosis in *C*. Bielschowsky x 480.

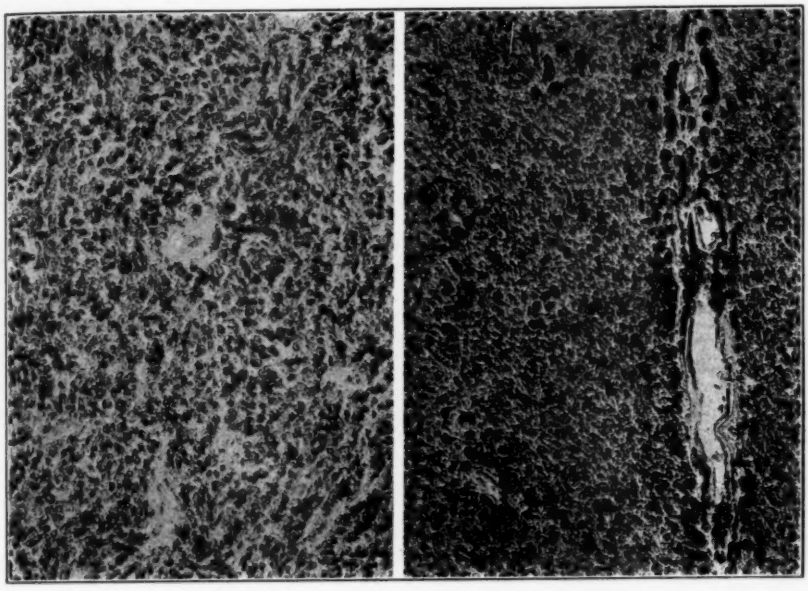

Fig. 4A Fig. 4B

Fig. 4A (Case 1)—Almost complete absence of fat in the pyramidal pathways from a case of amyotrophic lateral sclerosis treated with Vitamin E. Compare with *Fig. 4B* from an untreated case showing lipoid deposits throughout and in the perivascular spaces. Sudan III x 100.

completely chair-ridden and developed hoarseness, choking sensations and fibrillations of the tongue.

Neurological examination disclosed: a shuffling, unsteady gait with bilateral foot-drop; generalized fibrillations and marked atrophy in the intrinsic hand muscles, forearms, thighs and legs; hyperactive deep reflexes with diminished abdominal and cremasteric reflexes but no other pathological reflexes; bulbar speech and atrophy and fibrillation of the tongue.

Laboratory Data: negative except for marked spondylitis of the cervical and dorsal spine.

Course: Shortly after admission the patient received alpha tocopherol and the other ingredients from May 3, 1940 to June 7, 1940. Despite this, there was progression of the symptoms. On May 31, 1940 fibrillations were noted in the muscles of the palate and pharynx. On

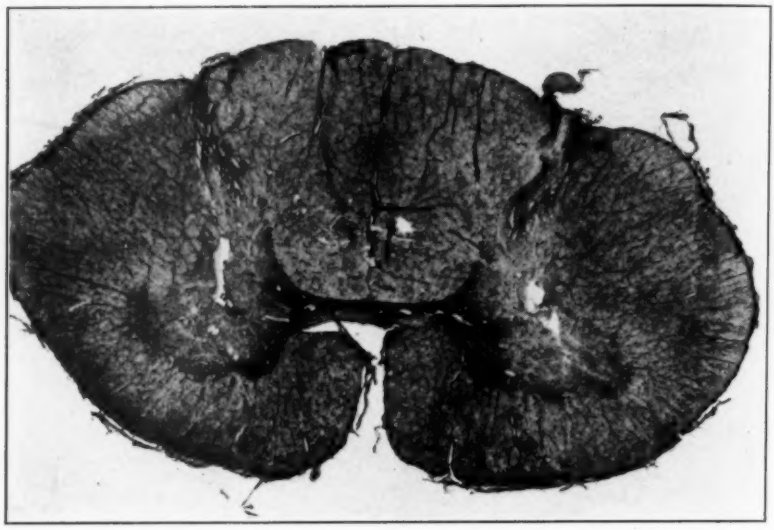

Fig. 5A

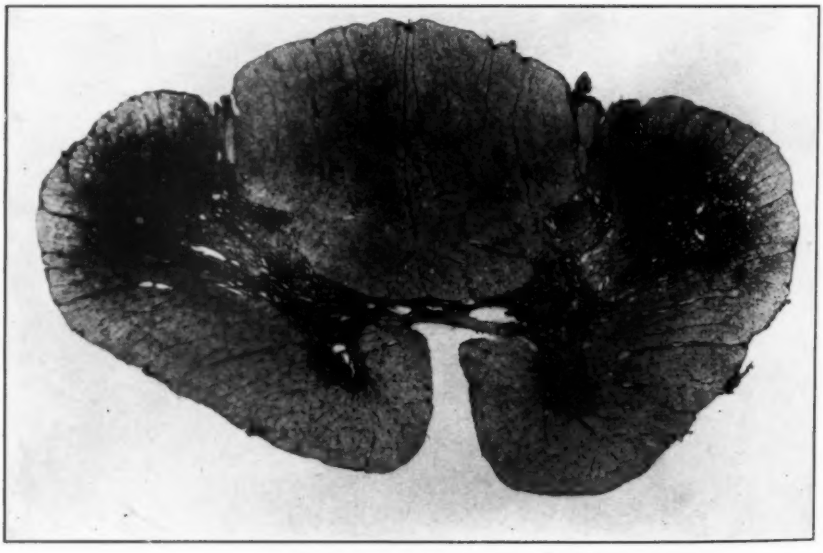

Fig. 5B

Fig. 5A (Case 1)—Lack of gliosis in the pyramidal tracts from a case of amyotrophic lateral sclerosis treated with Vitamin E. Compare with *Fig. 5B* from an untreated case of amyotrophic lateral sclerosis showing dense gliosis in the crossed pyramidal tracts. Holzer stain.

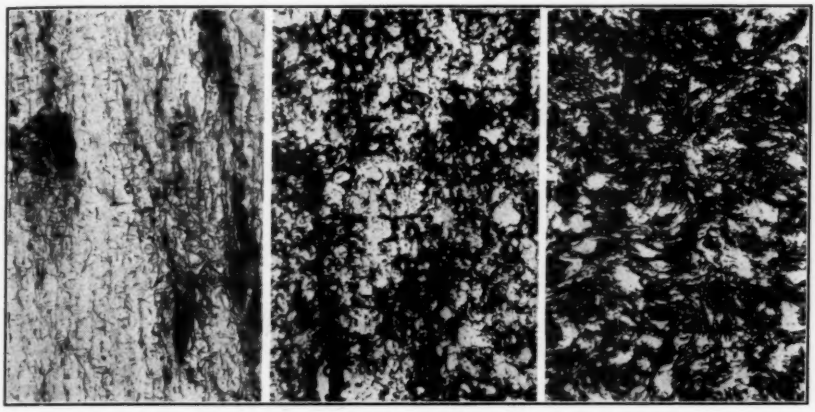

Fig. 6A Fig. 6B Fig. 6C

Fig. 6A (Case 1)—Slight insular gliosis from a treated case of amyotrophic lateral sclerosis. Compare with *Fig. 6B* from an untreated case and *Fig. 6C* from a case of descending degeneration. In *Figs. 6B* and *6C* the gliosis is dense, more so, however, in the case of descending demyelinization. Holzer x 200.

August 1, 1940 the patient became dysphagic, dyspneic and orthopneic and died of upper respiratory paralysis.

Autopsy report—The motor, premotor and parietal cortex and the internal capsules, peduncles and pons appeared normal. The pyramids of the *medulla oblongata* stained normally but an occasional swollen myelin fiber was noted. The nerve cells of the nucleus ambiguus and the 12th nerve nucleus were diminished in number and showed all types of pathological changes such as chromatolysis, shrinkage, pyknosis, corkscrew processes or complete disintegration.

Spinal cord: In the myelin sheath preparation, there was a very slight pallor of the crossed pyramidal tracts best seen in the thoracic regions (Fig. 7A). With high power, however, there were small islands of slight rarefaction of the myelin fibers in the crossed pyramidal tracts. A few were disintegrated but most of the changes consisted of swelling. Occasional swelling of myelin was also found in parts of the apparently uninvolved crossed pyramidal and ventrolateral tracts. The axis cylinders in the Bielschowsky preparation showed slight destructive changes, insular in distribution and less marked than in untreated cases of amyotrophic lateral sclerosis. Slight swellings were present in the unaffected parts of the pyramidal tracts. In the Sudan III preparation, the involved

Fig. 7A

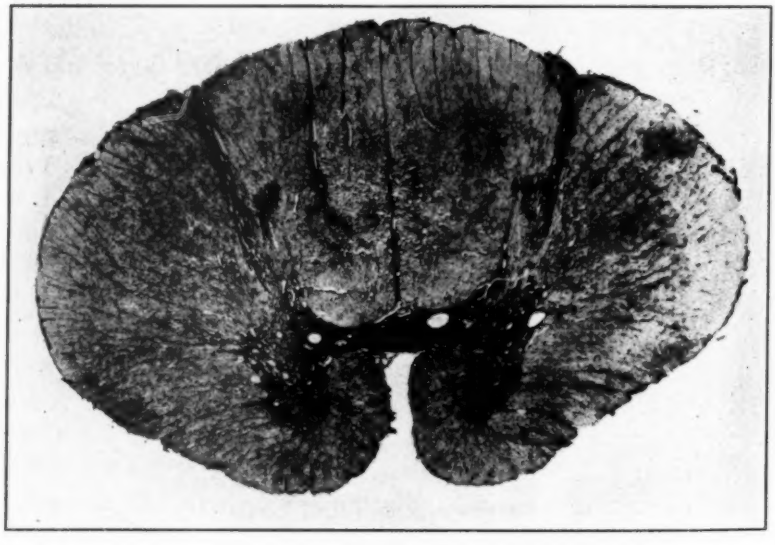

Fig. 7B

Fig. 7A (Case 2)—Notice presence of very slight demyelinization in the pyramidal pathways from a treated case of amyotrophic lateral sclerosis. Myelin sheath stain. *Fig. 7B* (Case 2)—Absence of dense gliosis in the crossed and direct pyramidal tracts from a case of amyotrophic lateral sclerosis treated with Vitamin E. Holzer stain.

pathways showed slight deposition of fat droplets in the crossed pyramidal tracts. These fatty deposits were less marked than in the untreated cases. In the Holzer preparation, there was only a very slight insular and perivascular gliosis in the crossed pyramidal tracts (Fig. 7B). In the cresyl violet preparation, there was a slight astrocytic proliferation in the involved pathways. The anterior horn cells were decreased in number, diminished in size and showed chromatolytic changes or pyknosis.

Comment: The involved pathways showed less changes in the myelin, axis cylinders and glia than usually seen in untreated cases of amyotrophic lateral sclerosis. The lipoid deposits were also less marked. There was hardly any gliosis and the little that was present was limited to the crossed pyramidal tracts. The illness in this instance only lasted 2 years and 7 months. The bulbar nuclei and the anterior horn cells were severely diseased and apparently uninfluenced by this form of treatment.

CASE 3—R.C., a man, aged 44, was admitted to this hospital on October 18, 1937 with a history of "twitches" in the muscles of the hands, arms and legs since 1934. One year later he was unable to walk unassisted.

Neurological examination disclosed: a spastic gait when supported; marked atrophy and fibrillations of the muscles of the shoulders, arms, hands and lower extremities; loss in muscle power throughout; marked hyperreflexia in the upper and depressed reflexes in the lower extremities; diminished abdominals and absent cremasteric reflexes.

Laboratory Data: negative.

Course: During the first year of his stay in the hospital, there was practically no progression of the symptoms. In November 1939 there developed respiratory difficulties. The patient received alpha tocopherol and the other ingredients from February 7, 1940 until June 12, 1940 when he expired.

Autopsy report—The motor, premotor and parietal cortex, the internal capsule, peduncles and pyramids in the pons appeared normal.

In the *medulla oblongata,* there was a faint pallor of the pyramids. With higher magnification, there was slight disintegration or swelling of single myelin fibers. The nerve cells of the 12th nerve nuclei were diminished in number and chromatolytic. Less severe changes were found in the nerve cells of the nucleus ambiguus.

Spinal cord: There was hardly any pallor in the crossed pyramidal tracts in the myelin sheath preparation. With higher magnification, most of the myelin sheaths in the pyramidal pathways appeared well preserved. A few, insular in distribution, were disintegrated, swollen or showed variability in contour. Occasional swollen sheaths were also found in the apparently unaffected pyramidal tracts. In the Bielschowsky preparation, the axis cylinders in regions of destroyed myelin were broken-down, swollen and occasionally had a corkscrew appearance. Some of the axis cylinders in the unaffected parts of the pyramidal tracts were swollen. In the Sudan III preparation, only a few fat droplets were found in the involved pathways. In the Holzer preparation, the involved pathways showed a very slight perivascular gliosis, insular in distribution. In the cresyl violet preparation, the affected pathways showed a slight astrocytic proliferation. The anterior horn cells especially those in the ventro-lateral and ventro-medial groups were markedly decreased in number. Those present disclosed extensive chromatolytic changes, shrinkage and pyknosis.

Comment: The myelin sheath destruction in the pyramidal and other ventro-lateral tracts and the gliosis was less extensive than in untreated cases of amyotrophic lateral sclerosis. Although the illness lasted six years, the pathological process was less marked than in cases of shorter duration.

CASE 4—R.F., a woman, aged 53, was admitted to this hospital on February 21, 1941 with a history of dysphagia and speech difficulty since December 1939. In March 1941, there appeared paresis of the upper extremities, difficulty in chewing, occasional "twitching" of the hands and left thigh muscles and atrophy of the shoulder muscles.

Neurological examination disclosed: a spastic gait; paresis of the upper extremities; atrophy of shoulder girdle and thenar muscles; fibrillations of neck muscles and left trapezius; total areflexia except for the presence of a slight right KJ; defective right plantar response with a positive Babinski sign on the left and absent abdominals; paresis of the motor 5th; a right supranuclear facial paresis; difficulty in swallowing; slow and nasal speech; limitation in the movement of the tongue with atrophy and fibrillations.

Laboratory Data: essentially negative.

Course: The patient received alpha tocopherol and the other ingredi-

ents. Despite treatment, the patient's illness progressed. She became completely aphonic, developed marked difficulty in swallowing, and expired on June 15, 1941.

Autopsy Report—Only sections of the brain stem and spinal cord were obtained.

Medulla oblongata: There was no demyelinization of the pyramids. With higher power, however, there was an occasional swollen or destroyed myelin sheath. The nerve cells of the ambiguus and 12th nerve nuclei were diminished in number and showed shrinkage, pyknosis, chromatolysis and shadow-like appearance.

Spinal cord: Demyelinization could not be detected with the naked eye. With high power, however, occasional destruction and variation in the size of single myelin fibers could be noted. Some were swollen and fragmented. This process, as in other instances, was insular in distribution. Occasional swelling of a myelin sheath could be detected in regions where the pyramidal tracts appeared intact. In the Bielschowsky preparation, the axis cylinders in the islands of demyelinization showed swelling, knob-like projections and corkscrew processes. In other regions of the pyramidal tracts, occasional swelling of the axis cylinders were also noted. In the Sudan III preparation, there were hardly any fat droplets in the involved pathways. In the Holzer preparation, gliosis could not be detected with the naked eye. In the slight areas of myelin sheath destruction, however, there was a faint, patchy, insular, perivascular gliosis.

Comment: This patient received Vitamin E therapy for a period of about seven and one-half months without any improvement in the neurological picture. The histopathological process of the myelin sheaths, axis cylinders, and glia in the spinal tracts showed a distinct difference when compared with those in the untreated cases.

CASE 5—H.F., a woman, aged 70, was admitted on February 3, 1941 with a history of progressive weakness of the extremities since September 1939. In November 1939 there developed dysphagia, regurgitation of food through the nose and excessive salivation.

Neurological examination disclosed: weakness, atrophy and fibrillations of the muscles of the upper extremities and sternocleidomastoids; hyperactive reflexes with bilateral Hoffman and defective plantar response; palatal paresis; defective gag reflexes and dysphagia; marked dysarthria, sialorrhea, atrophy and fibrillations of the muscles of the tongue.

Laboratory Data: negative.

Course: Patient received alpha tocopherol and the other ingredients from February 5, 1940 until April 14, 1940. The condition remained unaffected by the therapy and the bulbar signs progressed. The patient expired on October 8, 1940.

Autopsy Report: Only the brain stem and spinal cord were removed.

Pons: There was a faint pallor of the pyramids. With high power, occasional swelling, slight disintegration and variation in size were noted in a few fibers.

Medulla oblongata: There was a slight demyelinization of both pyramids with changes similar to those seen in the pons. In the cresyl violet preparation, the nerve cells of the ambiguus and 12th nerve nuclei were diminished in number and showed chromatolysis, vacuolization and shrinkage.

Spinal cord: There was slight demyelinization of both crossed pyramidal tracts best noted in the cervical regions and much less in the lumbosacral region. With high power, small islands of fibers in the crossed pyramidal pathways disclosed disappearance of myelin, swelling, disintegration and variations in size. Occasional swelling of a single myelin fiber was noted in apparently unaffected parts of the pyramidal tracts. In the Bielschowsky preparation, a few of the axis cylinders, especially in the islands of myelin sheath destruction, were swollen, broken-down and had a corkscrew appearance. In the Sudan III preparation, there were only a few fat granules in one region of the right crossed pyramidal tract. In the Holzer preparation, gliosis could not be seen with the naked eye; with higher magnification, a few islands of slight perivascular gliosis were noted in the involved regions. In the cresyl violet preparation, the anterior horn cells were diminished in number and showed loss in chromatin, pyknosis and sclerosis or severe cell changes.

Comment: This patient was treated with large doses of Vitamin E without clinical improvement. Histopathologically, demyelinization and destruction of axis cylinders and gliosis were slight.

CASE 6—T.R., a man, aged 54, was admitted to this hospital on July 2, 1940 with a history of increased salivation, difficulty in manipulating the tongue and in pronouncing the letter "L" and dragging of the left foot since February 1939. Later he experienced "jumping" sensation in the trunk and in the upper and lower extremities. In March 1940 speech became unintelligible and he could no longer move his tongue from

side to side or protrude it beyond the teeth.

Neurological examination disclosed: a spastic gait; weakeness of extremities with atrophy and fibrillations, especially in the muscles of the thenar and hypothenar eminences; generalized hyperreflexia with bilateral Hoffman, patellar and ankle clonus; complete palatal paresis; a speech limited to grunts; atrophy and fibrillations of the tongue muscles.

Laboratory Data: negative.

Course: The patient received alpha tocopherol and the other ingredients from August 2, 1940 until September 12, 1940. He was unable to swallow and had to be fed through a nasal catheter. After Vitamin E therapy, he was able to swallow a little but this function failed again. Finally the patient became bed-ridden and expired on February 4, 1941.

Autopsy Report: Only the spinal cord was obtained. In the myelin sheath preparation, there was a slight demyelinization of the right and very slight pallor of the left crossed pyramidal tracts (Fig. 8A). The myelin sheaths of this pathway were partially destroyed, especially on the right. Occasional swelling of myelin sheaths were noted in parts of the unaffected pyramidal tract. In the Bielschowsky preparation, the corresponding axis cylinders on the right were broken-down, swollen, had knob-like projections and a corkscrew appearance. On the left side, moderate axis cylinder destruction was present only in the small islands of myelin sheath degeneration. In the Sudan III preparation, fatty accumulations were present in both pyramidal tracts; a few fat droplets were present in the direct pyramidal, Holweg and ventro-spino-thalamic tracts. In the Holzer preparation, there was a dense gliosis in the right crossed pyramidal (Fig. 8B) and left lateral spino-thalamic tracts, and a slight gliosis in the left crossed pyramidal tract (Fig. 8B). In the right crossed pyramidal tract, astrocytic proliferation was more marked than on the left. This was best noted where there was severe myelin sheath destruction. The anterior horn cells were diminished in number, shrunken and showed loss in chromatin, shadow-like appearance or complete disintegration.

Comment: The pathological process in this instance was more extensive on the right side of the cord, as evidenced by the myelin sheath and axis cylinder destruction, the heavy deposits of lipoid and the extensive gliotic process. In the other half of the cord, the pathological process was very slight and almost identical with the process in the cases with little cord involvement.

Fig. 8A

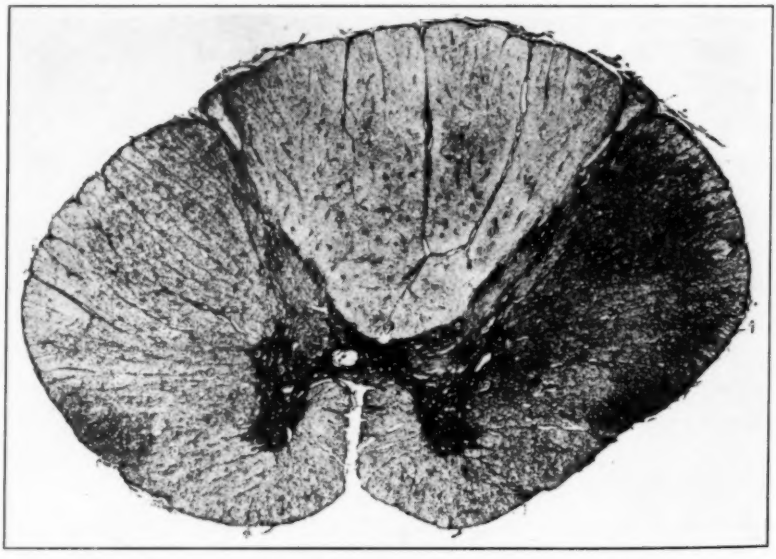

Fig. 8B

Fig. 8A (Case 6)—Transverse section showing slight pallor of the left and demyelinization in the right crossed pyramidal tracts. Myelin sheath stain.
Fig. 8B (Case 6)—Gliosis present only in the right crossed pyramidal tract but absence of gliosis in the left, except for the left lateral spinothalamic tract. Holzer stain.

II—CASES TREATED WITH VITAMIN E, SOME INADEQUATELY, WITHOUT SIGNIFICANT CHANGES IN THE INVOLVED PATHWAYS.

CASE 7—F.J., a man, aged 53, was admitted to this hospital on December 25, 1938 with a history of weakness of the legs since March 1938. This progressed and the patient finally was unable to walk without the use of a cane. In August 1938 he experienced spasms of the muscles of the thighs, and shortness of breath when speaking.

Neurological examination disclosed: a spastic gait when assisted in walking; marked fibrillations and atrophies of the muscles of the lower extremities, shoulders, abdomen and back; weakness in the extensor muscles of the legs; hyperactive tendon reflexes throughout, defective plantar responses and absent abdominal reflexes.

Laboratory Data: negative.

Course: There was a gradual progression of symptoms with extension of the process to the upper extremities, tongue, pharynx and larynx. This patient did not receive intramuscular injections of alpha tocopherol but received from February 5, 1940 to February 20, 1940 two tablets of ephynal by mouth daily and 5 mgm. thiamin chloride without any improvement in the neurological signs. He expired on February 23, 1940.

Autopsy Report—The cortex, internal capsule and peduncles showed no abnormality. Extensive demyelinization of the pyramids with destruction of myelin and axis cylinders began in the medulla oblongata. The nerve cells of the nucleus ambiguus and of the 12th nerve nucleus were diminished in number, showed marked loss in chromatin or were sclerotic.

In the *spinal cord*, there was extensive demyelinization of the crossed pyramidal tracts with slight involvement of the direct pyramidal and other ventro-lateral tracts (Fig. 9A). The myelin sheaths and axis cylinders in the pyramidal tracts showed the usual destructive changes seen in amyotrophic lateral sclerosis. In the Sudan III preparation, these pathways were heavily loaded with fat granules. Single fat droplets were also scattered throughout the ventro-lateral tracts. In the Holzer preparation, there was a dense gliosis in the region of the crossed pyramidal tracts (Fig. 9B). In the cresyl violet preparation, there was a marked astrocytic proliferation in the involved pathways. The anterior horn cells were markedly diminished in number especially the ventro-medial

Fig. 9A

Fig. 9B

Fig. 9A (Case 7)—Demyelinization of crossed pyramidal tracts from a case of amyotrophic lateral sclerosis inadequately treated with Vitamin E. Compare with adequately treated cases—Figs. 1A and 7A. Myelin sheath stain.

Fig. 9B (Case 7)—Gliosis in region of crossed pyramidal tracts from the same case. Compare with adequately treated cases—Figs. 5A and 7B. Holzer stain.

and ventro-lateral groups. Those which persisted were shrunken and showed marked loss in chromatin and their processes.

Comment: This patient who received ephynal orally for only a period of 15 days did not show any clinical improvement. The histopathological picture did not differ much from the average untreated case of amyotrophic lateral sclerosis.

CASE 8—B.J., a man, aged 50, was admitted to this hospital on July 19, 1939 with a history of inability to pronounce words clearly since December 1938. This condition progressed so that he could barely be understood. In March 1939 there developed weakness in the right lower extremity and dysphagia.

Neurological examination disclosed: a slow, broad-based unsteady gait with dragging of the right foot; fibrillary twitchings of the muscles of the shoulders and neck; atrophy of the muscles of right shoulder, thenar eminences, and calf; difficulty in performing skilled acts; hyperactive deep reflexes with bilateral Hoffman, Rossolimo and Babinski signs; dysarthric and nasal speech and fibrillations and atrophy of the muscles of the tongue.

Laboratory Data: negative.

Course: For seven months prior to admission to this hospital, the patient received brewer's yeast tablets. At Montefiore the patient received orally from February 7, 1940 to May 10, 1940 two tablets of ephynal daily, 5 mgm. of thiamin chloride, 4 cc. of wheat germ oil, bile salts and cod liver oil with continued progression of symptoms. He developed pneumonia and died on May 13, 1940.

Autopsy Report: Only the brain stem and the spinal cord were obtained.

Medulla oblongata: In the myelin sheath preparation, there was a slight bilateral demyelinization of both pyramids, definitely less extensive than in untreated cases of amyotrophic lateral sclerosis. Disintegration of myelin sheaths and axis cylinders could be observed with high magnifications. The nerve cells of the 10th, 11th and 12th nerve nuclei were diminished in number and showed severe cell changes of Nissl, chromatolysis, disappearance of the Nissl substance, displacement of nuclei at the periphery and pyknosis.

Spinal cord: There was moderate demyelinization of the crossed pyramidal tracts with sparing of the direct. With higher power, there was swelling and some destruction of the myelin sheaths and axis cylin-

ders but not as much as in the ordinary cases of amyotrophic lateral sclerosis. In the Sudan III and Marchi preparations, the involved pyramidal tracts contained fatty deposits but not in the excessive amount seen in the untreated case of amyotrophic lateral sclerosis. In the Holzer preparation, there was a moderate gliosis in the crossed pyramidal tracts which was not as extensive as in the ordinary case of amyotrophic lateral sclerosis. In the cresyl violet preparation, the involved pathways contained proliferating astrocytes. The anterior horn cells were diminished in number; some were shrunken and pyknotic, others showed chromatolytic changes or were completely disintegrated.

Comment: This patient received Vitamin E orally for 3 months without any clinical effects. Histopathologically, however, the involved pathways did not show the extensive changes seen in the average untreated case of amyotrophic lateral sclerosis. This was especially true of the demyelinization and gliotic process. The diseased anterior horn cells were unaffected by the therapy.

CASE 9—K.A., a woman, aged 49, was admitted to this hospital on July 27, 1939 with a history of generalized weakness, fatigue, difficulty in speech, swallowing, chewing and choking episodes and nasal regurgitation since November 1938. Later she experienced "twitchings" of the muscles of the neck and anterior part of the chest.

Neurological examination disclosed: a slightly spastic gait; weakness of the deltoid and scapular muscles, right more than the left; atrophy of the shoulder muscles with fibrillation, hyperactive deep reflexes in the uppers with Hoffman signs and hypoactive reflexes in the lower extremities without pathological reflexes; hyperactive jaw jerks; bilateral weakness of the 5th, 7th, 9th and 12th cranial nerves; marked dysarthria and dysphagia, and marked atrophy and fibrillations of the tongue muscles.

Laboratory Data: negative.

Course: The patient received intramuscular injections of alpha tocopherol and the other ingredients from September 29, 1939 until September 24, 1940 with frequent interruptions. There was a gradual relentless progression of the symptoms with increasing weakness and frequency of dyspneic episodes and sialorrhea. She became stuporous and expired on November 26, 1940.

Autopsy Report—Only the medulla oblongata, pons and spinal cord were removed.

Fig. 10

Fig. 10 (Case 9)—Case of amyotrophic lateral sclerosis treated intensively with Vitamin E for 1 year, but with interruptions, showing demyelinization of the crossed pyramidal tracts. Myelin sheath stain.

Medulla oblongata: Both pyramids were demyelinated and contained honeycombed areas. The myelin sheaths showed various pathological changes such as disintegration, swelling and variations in size. In the cresyl violet preparation, the nerve cells of the 10th and 12th nerve nuclei were diminished in number and showed pathological changes such as chromatolysis, peripherally displaced nuclei, shrinkage or shadow-like appearance.

Spinal cord: Demyelinization was limited to the crossed pyramidal and slightly to the left direct pyramidal tract (Fig. 10). With high power, the crossed pyramidal tracts had a slight honeycombed appearance. There was destruction, swelling and variations in the size of the myelin sheaths. The axis cylinders of the involved pathways were either destroyed, thin, swollen or had corkscrew processes and bulbar terminations. In the Sudan III preparation, the involved pathways contained an abundance of fat globules; some were collected in the perivascular spaces. In the Holzer preparation, the crossed pyramidal tracts showed dense gliosis as seen in the average case of amyotrophic lateral sclerosis. Slight gliosis was also found in the left direct pyramidal tract.

In the cresyl violet preparation, the anterior horn cells especially the ventro-medial and ventro-lateral groups were extensively diminished in number; they showed chromatolytic changes, granular disintegration, shrinkage, pyknosis and occasional corkscrew processes.

Comment: This patient received intensive Vitamin E orally and parenterally without improvement for a period of one year. In contrast with some of the other cases that received Vitamin E, the pathological process in the pyramidal tracts did not differ from cases of amyotrophic lateral sclerosis that did not receive such therapy.

CASE 10—M.R., a woman, aged 62, was admitted to this hospital on September 13, 1939 with a history of weakness of the left hand and "twitchings" in the muscles since January 1939. This condition progressed and spread to both upper and lower extremities.

Neurological examination disclosed: a spastic gait; weakness of hands, forearms, and lower extremities; atrophy of hand and forearm muscles; fibrillations of thigh and shoulder muscles; generalized hyperreflexia with bilateral Hoffman and ankle clonus; absent abdominal reflexes and fibrillations of the tongue.

Laboratory Data: negative.

Course: The patient received alpha tocopherol intramuscularly and the other ingredients from February 24, 1940 until September 24, 1940 with interruptions. During this period, the patient developed difficulty in talking and swallowing. In addition to the previous findings, there was a bilateral Babinski. On June 5, 1941 she suddenly collapsed, became cyanotic and died in respiratory failure.

Autopsy Report: In the *premotor and motor regions*, a number of the pyramidal cells had a shadow-like appearance. The giant pyramidal cells of Betz were diminished in number and showed pathological changes such as slight shrinkage and absence of Nissl substance. The internal capsule and peduncles did not show areas of demyelinization with low power, but with higher power, rarefaction and destruction of myelin fibers were noted. In the Sudan III preparation, these pathways contained fat droplets.

In the *pons*, there was pallor of the pyramids and the myelin sheaths were fragmented, swollen and varied in size.

Medulla oblongata: At this level, both pyramids were completely demyelinated and severe changes were found in the myelin sheaths and

axis cylinders. In the cresyl violet preparation, the nerve cells of the 12th nerve nucleus were diminished in number, shrunken and showed pigment atrophy and severe chromatolysis. Similar changes were found in the nucleus ambiguus.

Spinal cord: There was extensive demyelinization of the crossed and direct pyramidal tracts throughout all segments. The cord had a honeycombed appearance and the myelin sheaths were severely destroyed. In the Bielschowsky preparation, the axis cylinders, although they showed swelling and bulbous terminations, were not as severely damaged as the myelin sheaths. Here and there, completely destroyed axis cylinders could be noted; some had a corkscrew appearance. In the Sudan III preparation, the involved pathways contained fatty deposits but not as much as in the untreated cases. In the Holzer preparation, there was a dense gliosis of the crossed pyramidal tract and slight in the region of the direct pyramidal tracts.

Comment: In this case, there was implication of the motor cortex and severe involvement of the pyramidal tracts extending from the internal capsule to the spinal cord. Although this patient received Vitamin E for a period of about seven months, the changes in the affected pathways were not much different from the untreated cases of amyotrophic lateral sclerosis.

Analysis of Material

Clinical Evaluation: These cases present a few clinical facts worth discussing. There were six males and four females, a distribution which conforms with observations that the incidence of amyotrophe lateral sclerosis is greater in males than females. The ages of these patients were: two in the fifth decade, four in the sixth, three in the seventh, and one in the eighth. The duration of the illness in most instances was between two and two and one-half years except Case 3 who lived six years after the onset of the illness and Cases 1, 4 and 5 who lived twenty, eighteen and thirteen months respectively.

The first six treated cases that showed a different histopathologic picture from the usual picture in non-treated cases disclosed severe atrophy and fibrillations of the muscles especially in the distal parts of the extremities, more so in the upper than in the lower. The pyramidal tract signs consisted of a generalized hyperreflexia in all, diminished or absent abdominal reflexes in Cases 1, 2, 3, 5 and 6, Hoffman in Cases

5 and 6, Babinski or allied signs only in Case 4. These cases ought not to be confused with progressive spinal muscular atrophy, a disease of anterior horn cells without pyramidal tract lesions, where there is widespread atrophy of muscles and absent or markedly diminished deep reflexes. Furthermore, the onset of the illness in progressive spinal muscular atrophy starts at a much earlier age and lasts much longer than in amyotrophic lateral sclerosis, at times from ten to twenty years. Kinnier-Wilson[11] and others recognize that atrophy of muscles in amyotrophic lateral sclerosis may become so extreme as to abolish or decrease the respective reflexes. "There is as it were a conflict between the respective tone-increasing and tone-reducing influences of supranuclear and nuclear lesions" (Kinnier-Wilson[11]). In an analysis of thirty-six other cases of this illness that came to necropsy, fifteen with severe demyelinization of the pyramidal tracts, because of the marked atrophies, disclosed diminished or absent reflexes. It should also be emphasized that most of the cases in this presentation as in the normal cases of amyotrophic lateral sclerosis died because of involvement of the bulbar nuclei, a process which rarely occurs in progressive spinal muscular atrophy.

Kinnier-Wilson who is inclined to place progressive spinal muscular atrophy and amyotrophc lateral sclerosis in the same group states "difficult as it is to reach a firm conclusion, the lesions of the Charcot type (amyotrophic lateral sclerosis) are so characteristic, and when advanced, so different from those of nuclear amyotrophy (progressive spinal muscular atrophy), that in my opinion the fact outweighs other considerations; they comprise much more than the mere addition of upper to lower motor neuronic disease. While I consider this divergence more striking than the similarities, the occurrence of gradations from one to the other, and also in the direction of "subacute anterior poliomyelitis" must be admitted; not all of either kind run true to type. For *descriptive purposes* [underscored by Davison], however, it is best to take the two varieties together, inclusive of intermediate and aberrant clinical forms."

Of the ten cases, two (7 and 8) received ephynal by mouth; the others also received alpha tocopherol intramuscularly. Case 7 received the treatment only for a period of 15 days. The others were treated from five weeks to seven and one-half months. Cases 9 and 10 were treated for one year and seven months respectively but with interruptions. As will be seen this may have had some relationship to the histopathologic changes. None of these cases except Case 6 showed any

improvement in the neurological symptoms.

Histopathologic Evaluation: Nerve cell changes: The histopathological changes in the involved nerve cells of the medulla oblongata (usually 10th and 12th nuclei) and anterior horn cells in the spinal cord were the same in the treated as in the untreated cases of amyotrophic lateral sclerosis. This was true both in regards to the number and character of the nerve cell changes. The involvement of the bulbar nuclei and the progress of the changes in these nerve cells resulted in death in most of these cases.

Pathway changes: On the other hand, definite changes were present in the myelin sheaths, axis cylinders, fat and glia.

In Cases 1, 2, 3, 4, 5 and 6, or 60 per cent of the cases, the pathological process in the involved pathways of the central nervous system especially of the spinal cord differed entirely from the untreated cases. In these, except Case 6, demyelinization of the crossed pyramidal tracts in the myelin sheath preparation could hardly be detected with the naked eye (Fig. 1A). This was not true in the untreated cases where the demyelinization stands out prominently (Fig. 1B).

Occasionally a case of amyotrophic lateral sclerosis may show little demyelination in the pyramidal pathways. Two such cases were found among the other thirty-six cases that came to necropsy. One of these turned out to be a case of spastic pseudosclerosis. The diminution of demyelinization in the first six consecutive cases that were treated certainly could not be a mere coincidence. Furthermore, even the other four less adequately treated cases showed changes which were slightly less severe than in the ordinary run of amyotrophic lateral sclerosis.

With higher magnification, the involved myelin sheaths, usually grouped in small islands, were fragmented or swollen (Fig. 2A). When compared with myelin sheath changes in untreated cases, it can be definitely stated that this process was not 1/10th as extensive as in the average case of amyotrophic lateral sclerosis (Fig. 2B). Occasional swelling of myelin sheaths could also be detected in parts of the pyramidal tracts which did not appear demyelinated (Fig. 2C). In Case 6, the right pyramidal tract was demyelinated and destruction of myelin sheaths in this pathway was more extensive (Fig. 8A).

The pathological process in the axis cylinders except those of the right pyramidal tract in Case 6 was essentially limited to the islands of involved myelin sheaths. Here the changes, although much less intense

than in the untreated cases, consisted of swelling, slight fragmentation, bulbous terminations, and corkscrew appearance (Fig. 3A). Various degrees of swelling of the axis cylinders were also noted in parts of the pyramidal tracts which did not appear demyelinated.

In the Sudan III preparation, the amount of fatty deposits differed in these six treated cases. There were hardly any fatty deposits in the lateral or anterior pyramidal tracts in Cases 1 and 5 (Fig. 4A). Cases 2, 3 and 4 had less fat than the untreated cases, while in Case 6, the fatty contents did not differ much from the untreated cases.

Most of the outstanding changes, however, were noted in the glia tissue. In the untreated cases of amyotrophic lateral sclerosis, there was a dense gliosis in the involved pathways easily detected with the naked eye in the Holzer preparation (Fig. 5B). In these six treated cases, except for the right pyramidal tract in Case 6 (Fig. 8B), the gliosis could hardly be observed with the naked eye (Fig. 5A). With higher magnification, however, small perivascular islands of gliosis (Fig. 6A) were noted in the region of the involved myelin sheaths and axis cylinders.

In the seventh case, which was treated for only a short period of time (15 days) with ephynal by mouth, the myelin sheaths, axis cylinders, fat content and glia reaction did not differ from the untreated cases of amyotrophic lateral sclerosis. In cases 8, 9 and 10, the destruction of myelin sheaths, axis cylinders and the gliosis were not much different, although slightly less than in the untreated cases. In Case 8 the fatty accumulations in the affected pathways were definitely less than in the untreated case. The gliotic process in these cases was moderate in degree and slightly less intense than in the ordinary cases. In order to be on the conservative side, the changes in these cases were considered about the same as those found in untreated cases.

Certain factors may have played a role in the histopathological changes of these three cases. In Case 8 the patient received ephynal orally, but did not receive alpha tocopherol intramuscularly. Cases 9 and 10 were treated for one year and seven months respectively including intramuscular injections of alpha tocopherol, but the treatment was interrupted several times. This may have influenced the lack of improvement in the involved pathways. The age, the duration of the illness and the time the treatment was begun in these instances did not differ from the other treated cases.

Factors influencing the changes in the affected pathways: As was previously demonstrated (Davison[12]) in untreated cases of amyotrophic lateral sclerosis, the diseased process affects the upper and lower motor neurons. The upper motor neuron can be involved, either at its point of origin in the giant pyramidal cells of Betz or anywhere along its course. The upper motor neuron lesion is most pronounced in the spinal cord and is characterized by destruction of the myelin sheaths and axis cylinders and a dense glial scar. Once the myelin sheaths and axis cylinders in the involved pathways are completely destroyed, their regeneration is problematic. Some observers are under the impression that regeneration of axons in involved pathways of the spinal cord may take place under favorable conditions in a manner similar to regeneration of axons in peripheral nerves. By the new methods of neurofibrillar study, it has been demonstrated that the production of new fibers, clubs, cones and ramified axons may occur in various lesions of man and animals. These findings, while they demonstrate signs of repair comparable in principle with those of the central stump of the peripheral nerve, do not contradict the conception of the impossibility of complete regeneration of axis cylinders in the spinal cord. These later investigations have also demonstrated that after a certain length of time the restoration of the axon in the spinal cord stops, that the axon atrophies and that finally the nerve sprouts break down completely.

On the basis of the above investigations, it can hardly be expected that completely destroyed myelin sheaths and axis cylinders in the spinal cord should regenerate. In the six out of the ten cases of amyotrophic lateral sclerosis adequately treated with Vitamin E there was no question that the involved myelin sheaths and axis cylinders were less affected when compared with similar preparations of untreated cases. When I[13] observed similar improvement in the cases of subacute combined degeneration adequately treated with liver, I then postulated that axis cylinders may undergo a reversible reaction provided they are not severely affected and if the patient receives early and adequate treatment. Can this explanation also be applied to amyotrophic lateral sclerosis? This cannot be answered as easily as in subacute combined degeneration. There is a possibility in amyotrophic lateral sclerosis, as in subacute combined degeneration, of a reversibility of the reaction if the axis cylinders are not severely destroyed. In other words, damaged but not completely destroyed axis cylinders, under favorable circum-

stances, may regenerate or be restored nearly to their normal state. This is the only possible explanation that can be offered from the above observations. Under these circumstances, clinical improvement in the neurological signs and symptoms in the above cases should have been expected. This, as already stated, did not occur. How can this discrepancy be explained? The possibility that these patients did not receive adequate quantities of Vitamin E and/or were not treated sufficiently early must be considered. In some instances of amyotrophic lateral sclerosis, besides the lack of Vitamin E which may cause the disease, there is the possibility as suggested by Wechsler,[1] of another unknown factor, which may play a role in the absorption of the vitamin. These are questions which so far have not been settled and cannot be answered with certainty. It is possible that in some instances, early and adequate administration of Vitamin E may arrest the process in the involved myelin sheaths and axis cylinders and may restore their function provided they are not completely damaged.

The lessened or almost complete disappearance of fatty deposits in the treated cases can be explained on the basis that the Vitamin E treatment may have resulted in a decline or cessation of the pathologic process, thus helping towards the removal of the products of disintegration.

The absence of intense gliosis or the regression of the gliosis in the treated cases appears disturbing for the contrary would be expected in areas of myelin sheath and axis cylinder repair. In a number of cases of subacute combined degeneration that received adequate liver therapy studied by the author,[13] the improvement noted in the affected pathways was accompaniel by a dense gliosis. There is a remote possibility that the restoration or reversion to a normal or nearly normal glia reaction as seen in the treated cases of amyotrophic lateral sclerosis is parallel to the observed restoration of the myelin sheaths and axis cylinders. If this should be true, then it may be postulated that the reversibility of reaction took place all along the line, affecting simultaneously and equally or nearly equally the damaged myelin sheaths, axis cylinders and glial tissue.

One other disturbing factor in this study were the changes in the nerve cells in the involved bulbar nuclei and anterior horns which did not differ in the treated from the untreated cases. Clinically, however, Wechsler[1] observed that the fibrillations and the bulbar signs especially the recent ones cleared up, whereas, the pseudobulbar symptoms re-

sponded less well or not at all.

There are still many questions regarding the treatment of amyotrophic lateral sclerosis which will have to be answered. While the efficacy of Vitamin E therapy in this disease is still problematic, the above histopathologic findings and the clinical (Wechsler[1]) evidence indicate that this form of treatment should be continued experimentally.

Summary and Conclusions

Ten cases of amyotrophic lateral sclerosis were treated with Vitamin E and alpha tocopherol and except for one, none responded clinically to this form of treatment.

Histopathologically, however, in six of the intensively treated cases the destruction of the myelin sheaths and axis cylinders was found to be much less intense than in the untreated cases. The dense gliosis which is usually present in amyotrophic lateral sclerosis was diminished or almost absent in those that received Vitamin E. The lessened myelin sheath and axis cylinder destruction and the faint gliosis in these instances were perivascular and insular in distribution. In one of these (Case 6), the lessened changes were limited to one side of the cord only. The nerve cells of the involved bulbar nuclei and anterior horns remained unchanged and showed no signs of reversibility. The ultimate cause of death was bulbar in nature.

The histopathologic processes in the other 4 less intensively treated cases, although less extensive, were considered about the same as those found in untreated cases.

There is a possibility that Vitamin E therapy resulted in a reversal of the reaction of degeneration affecting simultaneously and nearly equally the damaged myelin sheaths, axis cylinders and glia in amyotrophic lateral sclerosis.

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TREATMENT OF PROSTATIC CARCINOMA*

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We stand to-day at the fascinating period where better control of prostatic cancer appears at hand. This disease has emerged from its earlier position as an almost hopeless type of cancer to a present situation where some measure of control seems possible in 50 per cent of cases (Huggins). What the future holds we do not know. The treatment so ably developed by Dr. Huggins may eventually lead to complete understanding and cure of this lethal disease.

The dramatic improvement following orchidectomy in some patients with prostatic cancer gives me the same thrill that I experienced when twenty-five years ago I saw the first metastasis from a teratoma testis disappear under the radium pack and the first bladder cancer, to which radium was applied, vanish.

Because orchidectomy with any added hormone medication is far from being one hundred per cent successful it is possible that some combination of orchidectomy and the past not wholly ineffective treatments should be used.

Allow me to review very briefly the pre-orchidectomy period.

Radiation treatment by means of radon-bearing needles or radon seeds has afforded control in twenty-one of 352 cases (6 per cent) for periods of between five and nineteen years. These patients are, so far as can be seen, free of cancer. Radiation treatment has been of value in maintaining the patency of the urethra and so enabling a patient to empty his bladder during the years he has to live. Deep x-ray therapy has been of little use in controlling the disease.

Radical removal of the small prostatic cancer has likewise effected a cure in a small percentage of prostatic cancers. This operation, devised and elaborated by Young, has been done by many urologists–Smith, Hinman and others for many years.

* Read December 3, 1942 at the Stated Meeting of The New York Academy of Medicine in association with the Section of Genito-Urinary Surgery.

So is summarized in half a page the results of a prodigious amount of work covering twenty-five years.

In the pre-orchidectomy period there were four developments all of which have carried over to and been extremely valuable in the orchidectomy period. These are:

1. Aspiration biopsy.
2. Transurethral resection.
3. Recognition that prostatic carcinoma often metastasizes to bone.
4. Acid and alkaline serum phosphatase determination.

Aspiration biopsy of the prostate was developed at the Memorial Hospital and after using a series of different puncturing instruments a simple long spinal type aspirating needle was found best. It was found that such a needle could be introduced through the perineum into the prostate with a guiding finger in the rectum and by means of suction a plug of prostatic tissue large enough for staining could be obtained. In this way early and puzzling cases could be accurately diagnosed. The method is about 70 per cent successful. The type of carcinoma cannot, however, be determined in the specimen.

Transurethral resection has had wide use and is of much value in coping with that most troublesome symptom of prostatic cancer, urinary retention. Two things are accomplished by it: first, relief of retention; second, a pathological specimen is obtained for accurate diagnosis. In the hands of some urologists it has been done multiple times during the period which the patient lived with ever-recurring retention.

Over the course of the years it has been found and noted in many instances that prostatic carcinoma very often metastasizes to bone. These metastases generally are osteoplastic and therefore cast a dense shadow on the x-ray film. Whether these metastases be venous or lymphatic, they occur most often in the lumbar spine and pelvis.

The determination and meaning of the acid and alkaline serum phosphatase date back to 1935 when Kutscher and Wolberg[1] reported that there was acid phosphatase in the prostate.

Gutman, Sproul, and Gutman[2] in 1936 reported both acid and alkaline phosphatase in bones which were the site of prostatic cancer metastases. Two weeks after this publication Woodard (unpublished) found excess acid phosphatase in the serum of a patient with metastatic carcinoma of the prostate. The Gutmans published three papers,[3, 4, 5] two in 1938 and one in 1939 discussing the elevation of acid phosphatase in

the serum of patients with metastasizing carcinoma of the prostate.

Barringer and Woodard[6] published in 1939 a paper, read before the American Association of Genito-Urinary Surgeons in May 1938, giving findings in a number of cases of prostatic carcinoma and suggested that: "There is apparently a direct relation between the laying-down of bone in prostatic carcinoma and the blood phosphatase. The determination of the blood phosphatase may have some value in diagnosing osteoplastic metastases, possibly before such metastases are revealed by radiograph. It unquestionably is of value in the differential diagnosis of the source of a bone metastasis."

In 1941 Woodard and Higinbotham[7] discussed the changes in the acid and alkaline phosphatase of patients with prostatic cancer following roentgen therapy.

The Gutmans' last paper[8] on the "Theory and application of the serum 'acid' phosphatase determination in metastasizing prostatic carcinoma" was published in October 1942.

Suffice it to say here that serum "acid" phosphatase is generally elevated if the prostatic carcinoma is of any size and the serum alkaline phosphatase is elevated if there are bone metastases. Therefore, we have a method of diagnosis and differential diagnosis of the prostatic carcinoma itself and of the bone metastases; we also have a method of estimating recessive changes in both of these.

The orchidectomy period has demonstrated that simple orchidectomy may in some cases cause complete recession of both the prostatic carcinoma and the bone metastases. This, of course, is revolutionary. The probable rationale is that the testicular hormone is necessary for prostatic activity. Remove the testis and one inactivates the prostate and also the prostatic carcinoma. Because metastases are controlled it is assumed that they possess metabolic attributes in some manner similar to those of the prostate. Suggestive evidence of this is that both prostate carcinoma and prostatic metastases contain "acid" phosphatase.

We know that some cancers are capable of performing the same functions as the normal tissues from which they arise. An example of this is the classic case of von Eiselberg quoted by Ewing,[9] in which myxedema followed total extirpation of the thyroid for cancerous goitre; but disappeared on the development of a metastatic focus.

That there must be other extra-testicular elements controlling both the prostatic carcinoma and the metastasis is evident because Huggins

reports regression in but 50 per cent of cases and we in considerably less. Assays of the urine of castrated patients show this. That is, in urine there are excreted 17-ketosteroids (androgen) and also estrogens. When the testicles are removed, the 17-ketosteroids, instead of decreasing, remain constant or may rise. This indicates that there is some other source of the 17-ketosteroids. We know that the adrenals are at least one other source of androgens.

Orchidectomy and Bone Metastases. We have had fifty cases in which orchidectomy has been performed. Because of various factors, in but twenty-eight of these cases are the records sufficiently complete to report. That is, in these twenty-eight cases the pathological examination is complete; pre- and many post-orchidectomy phosphatase examinations have been made and pre- and post-orchidectomy roentgenograms made, and the patients have survived a sufficient length of time after orchidectomy to enable some conclusions to be drawn.

Of these twenty-eight cases, seventeen had high alkaline phosphatase (indicating bone metastases) and nineteen had bone metastases shown by roentgenogram. In five of nineteen cases the bone metastases worsened, but in size and number. In one there was no change. In one there was extension of bone metastases in some areas and in others the metastases grew less dense. In two cases with atypical (osteolytic) bone metastases there was some healing, five and six months after orchidectomy. One had a metastasis to the tibia which was treated by deep x-ray therapy and orchidectomy. This showed almost complete recession six months later. The most satisfactory case had a metastasis to the femur, invading the soft parts. Eight months after orchidectomy there was evidence of remarkable healing (shown by roentgenogram and palpation). This is therefore our record to date of the effect of orchidectomy on bone metastasis. In about half there was increase in the bone metastasis. Given time a different picture may present itself.

Stilbestrol. Because castration is not a completely successful antiandrogen, stilbestrol is given in large daily doses (5 mg. daily by mouth) to reinforce the castration effect. In order to determine accurately the effect of stilbestrol, we have used it as the sole treatment in eighteen cases. Of these eighteen patients, seven had bone metastases. Four of the seven showed increase in both the size and number of bone metastases. Two probably developed metastases during the treatment. One had atypical (osteolytic) metastases which in four months showed in-

crease in density. At the present time it is impossible to tell whether this is a healing effect or not. Kohle, Ogden and Gilzoff report one case in which a roentgenogram "showed a marked diminution in the number and extent of the metastatic lesions as compared with previous examination."

But one of our eighteen patients had radon applications to his prostate followed by deep x-ray therapy. One had an orchidectomy at the end of his stilbestrol period (one year and two months). In all of the patients, including one in particular who had a great deal of back pain from dorsal and sacral metastases, pain was successfully controlled by stilbestrol. In this patient the back pain had not been at all affected by deep x-ray therapy. All of these patients gained in weight, one of them twenty pounds in several months. One of them after a year on stilbestrol developed very active skull metastases with much pain in the occipital region and face. In this patient orchidectomy entirely controlled this pain but the patient had a stroke two months after his orchidectomy. In many of the patients the prostate carcinoma became smaller and softer.

In summary, stilbestrol controls pain, causes recession of the prostate growth and improves the general condition but rarely has any effect on the bone metastases. It should therefore be used only in combination with orchidectomy.

Effect of Orchidectomy on Residual Urine: There is very little evidence that orchidectomy has any effect in controlling this symptom. A good many cases with residual urine have had transurethral resection because of imperative symptoms, both to enable the patient to empty his bladder and to obtain a specimen for pathological examination. It is probable that in many cases, once a patient can empty his bladder, orchidectomy is a vital factor in maintaining this power to empty the bladder, because in many patients both after orchidectomy and stilbestrol medication the prostate becomes markedly smaller and softer.

Pre-Orchidectomy Prognosis: Huggins, if I read him correctly believes that the adeno-carcinoma is the type which does best following orchidectomy and that the small cellular carcinoma as a rule does not do well. I can give no data on this point.

Value of Phosphatase in Establishing Prognosis: Sullivan, Gutman and Gutman[8] have made these observations: "Castration in every instance (with one explained exception) was followed by early precipit-

ous fall in serum acid phosphatase, often demonstrable after twenty-four hours. On the second post-operative day the mean decline in acid phosphatase was 55 per cent of the pre-operative level." In three cases of our own in which there was no lowering of the acid phosphatase, two died two months after orchidectomy.

Summary of Treatment: We believe that the following suggestions as to treatment of prostatic carcinoma are justified. Orchidectomy and stilbestrol medication should be the treatment in all cases of prostatic carcinoma. This therapy should be preceded by transurethral resection if urinary retention is a dominant factor. Transurethral resection is unnecessary to establish the diagnosis. Aspiration biopsy should be sufficient for this. If the prostatic carcinoma is small, confined to the prostate and peri-prostatic region, radiation of the prostate or the operation of total prostatectomy should be considered.

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PUBLIC HEALTH IN NEW YORK CITY

*A Retrospect**

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To present a satisfactory retrospect concerning public health in New York City is a difficult assignment, and in the time at my disposal I shall be able to deal briefly with only a few phases of the subject.

1800-1825

During the first quarter of the nineteenth century the city extended to about Canal Street. Shipping and trade were the chief occupations, and the artisans were largely independent workers. Manufacturing played only a minor role, and steam power factories did not become common until the forties and fifties. Housing conditions were favorable; gardens and orchards were common; there were no tenements. In the built-up portions of the city, a private company supplied water through wooden pipes laid beneath the streets; in other parts of the city private wells were in common use. Outdoor privies were the rule, and they were built over water-tight vaults which were emptied at intervals by the scavenger. Water closets did not come into use until after the introduction of Croton water in 1842. Judging from what reports, etc., are available, New York appears to have been a reasonably clean and tidy town during the first quarter of the nineteenth century.[1] The general death rate from all causes was about 25 per 1000 and the infant mortality ranged between 120 and 140 per 1000 live births. This first quarter of the century was relatively free of serious epidemics, though yellow fever appeared in 1805 and again in 1822.

1825-1850

The second quarter brought profound changes. The population growth became accelerated. With the introduction of steam power, fac-

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† On June 1, 1943 the author completes 39 years of distinguished service in public health work. Ed.

tories multiplied, and these attracted workers to the city. Immigration from Europe increased rapidly, at first from Ireland and during the late forties from Germany and other continental countries. The competition of the ever increasing immigrants lowered all standards of living. Wages, especially after the panic of 1837, were reduced, and again reduced. The housing situation became acute. To relieve the overcrowding the cheapest kinds of houses were built. Cellars were used as living quarters. All in all conditions became more and more insanitary.

In 1832 a severe epidemic of cholera caused 3500 deaths and a recurrence in 1834 carried off nearly 1000 victims. Finally just before the close of this second quarter, in 1849 cholera again ravaged the city causing over 5000 deaths. The first appearance of cholera, in 1832 gave renewed impetus to plans for a satisfactory and sufficient water supply, and these were finally carried through successfully in 1842 when the Coton Aqueduct was opened. An account of the many difficulties attending this important undertaking will be found in the August 1942 issue of the *Quarterly Bulletin* of the New York City Health Department.

The insanitary conditions which marked this second quarter are reflected in the steady increase in the infant mortality rate. By 1850 this had climbed to 180 per 1000 live births.[2]

The second quarter also marked the beginning of the campaign for pure milk for the people of this city. Perhaps you know that this was a by-product of a great temperance campaign, whose prime mover was a Mr. Robert Hartley. He soon discovered that distillers made money by selling to dairymen the mash remaining after whiskey was made. He investigated the cow stables which adjoined the distilleries, and discovered conditions so insanitary that it is hard to believe them today. Largely as a result of Mr. Hartley's exposé, The New York Academy of Medicine in 1848 appointed a committee to look into the milk situation. Despite the efforts of the Academy, and of other public spirited citizens, notably Frank Leslie, the publisher, it was not until nearly fifty years later that a wholesome milk supply was provided for the people of this city.

1850-1875

We return now to the beginning of the third quarter of the nineteenth century. The built up portions of the city had meantime extended

rapidly. There was considerable dissatisfaction concerning the filthy condition of the streets, and with the city's health administration. In 1851 an epidemic of smallpox caused 562 deaths and three years later cholera claimed over 2500 victims, and 1137 in 1866. Smallpox continued to ravage the city causing 664 deaths in 1865; 1662 in 1872 and 1889 in 1875. Even yellow fever reappeared, though there were only 9 deaths, in 1870. A committee of prominent citizens became active during the fifties and sixties, a committee in which Dr. Stephen Smith took a leading part. A detailed sanitary survey carried on under the auspices of this committee revealed revolting insanitary conditions. Filthy streets, filthy stables and cow barns, wretched slum housing, cellar dwellings, backyard tenements without light or ventilation, outdoor, insanitary privies, adulterated milk supplies, and generally high death rates. You can read it all in Stephen Smith's book *The City that Was.*[3]

I can perhaps add a bit of evidence of interest. Many of you may remember my friend the late Dr. William H. Guilfoy, formerly Registrar of Records. Dr. Guilfoy was born on the lower West Side, not far from Washington Market, in 1859. He told me that as a young lad, on rainy days he would hurry home from school, arm himself with a broom, station himself at near-by Broadway and there offer to sweep a path through the muck and filth so that a person could cross the street. "And many a nickel I picked up in this way."

In the early sixties the built-up portion of the city embraced about eight square miles and the population numbered nearly a million. Besides the insanitary conditions just mentioned there were a vast number of special nuisances. Thus there were nearly 200 slaughter houses, many of them in the most densely populated districts. To these places droves of cattle, hogs and sheep were constantly driven rendering the streets extremely filthy not only with animal excreta, but with the blood and refuse flowing from the slaughter houses. In certain populous sections there were establishments for fat and bone boiling, for cleansing entrails and curing tripe. The numerous stables and cow barns have already been mentioned. They brought the additional nuisance of manure heaps and the carting of this manure through the streets. In this connection some pictures taken from the Report of the Citizens' Committee may be of interest.[4]

It may be well, at this point to call attention to the great social and sanitary reforms inaugurated in England during the forties, fifties and

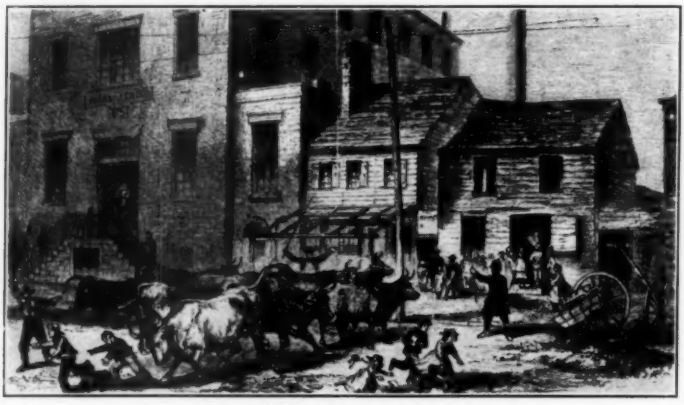

Fig. 1—The vicinity of a slaughter house during the 1850's. Note the public school.

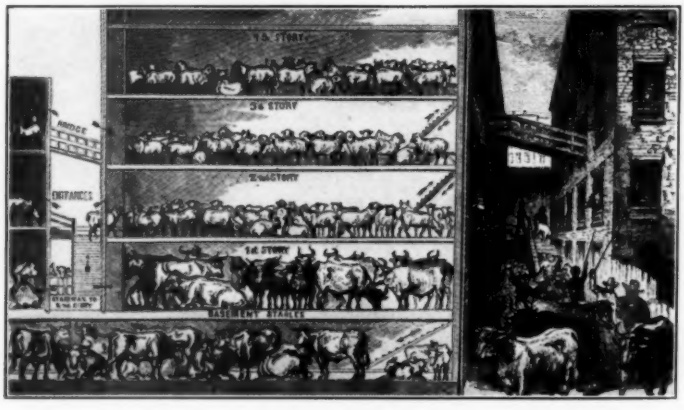

Fig. 2—Plan of a slaughter house. From the Report of Citizens' Association.

sixties of the last century. These may be said to have had their beginning in the reports published by John Howard concerning conditions in prisons, hospitals and lazarettos of Europe 1777-1789. But it was the repeated occurrence of devastating epidemics of cholera during the thirties which gave real impetus to the movement and here we find Edwin Chadwick, Florence Nightingale, John Simon, John Snow, Edmund Parkes, William Budd and the statistician William Farr making

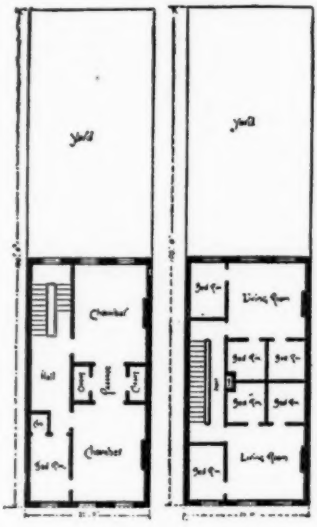

Fig. 3—A private dwelling remodelled into a tenement. One floor rearranged for two families. Inside bedrooms without light or ventilation.

very valuable contributions. The influence of these reforms manifested itself in this country in reforms urged in Massachusetts by Lemuel Shattuck, and in New York by the remarkable achievements of Stephen Smith and Dorman B. Eaton in connection with the work of the Citizens' Committee already mentioned.[4]

Let me return, therefore, to the accomplishments of this committee, for they became the basis of sanitary legislation throughout the country.

Prior to 1866 there were in this city four separate authorities devoted to the conservation of public health. Quoting from Stephen Smith,[3] there were:

"First, the Board of Health, composed of the Aldermen and Mayor. When this body was organized as a Board of Health it had supreme power, both in the abatement of nuisance and the expenditure of money. So much and so justly was this board feared, that Fernando Wood, while Mayor, refused to call it into existence during an epidemic of cholera, declaring that the Board of Health was more to be feared than the pestilence.

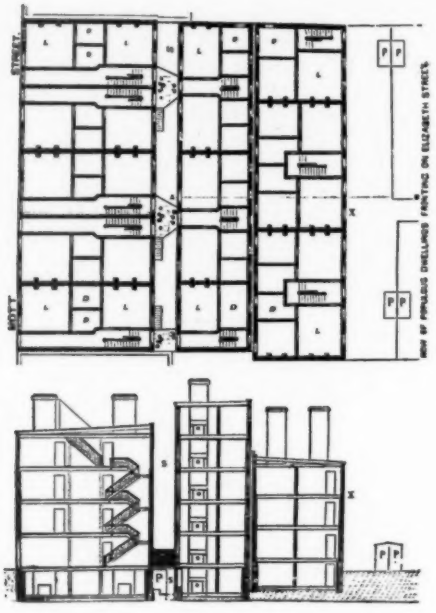

Fig. 4—Tenements occupying nearly the entire lot. One building faces the street at the left. Back of this is a narrow court, and then comes the rear tenement on the same lot, having windows only to the court.

Note a similar rear tenement on the lot in the rear.

"Second, the Commissioners of Health, composed of the Mayor and the Recorder, the City Inspector, the Health Commissioner, the Resident Physician, the Port Health Officer. This body had no adequate power and was perfectly useless both for good and evil.

"Third, the Resident Physician, whose duties were limited to visiting the sick poor.

"Fourth, the City Inspector, a most formidable official politically, for he had the right to expend annually $1,000,000 without "let or hindrance." His jurisdiction extended to the cleaning of the streets, gathering vital statistics, and preserving the public health by the appointment of health wardens for each ward.

"The committee's investigation showed that this department, the only one which actually exercised public health functions, was per-

meated with corruption, ignorance, and venality. The City Inspector was the lowest type of ward politician, the vital statistics were crude and unreliable, there was no pretense of cleaning the streets, and the health wardens were for the most part keepers of saloons."

As I read over the annual reports of the various City Inspectors,[5] I believe that Stephen Smith was a little unjust. Some of the officials appear to have been alert and competent health officers. For example John Pintard who served from 1804 to 1810 made recommendations on the following: Ample supply of pure potable water; drainage of low marsh land; construction of common sewers; the interment of dead bodies within the city; prohibiting the habitation of damp cellars; providing increased accommodations at Bellevue Hospital; enforcement of accurate returns of death; and regulations regarding the quarantine of vessels coming from southern ports during the months of July, August and September.

City Inspector Dunnell in 1838 was the first to advocate maintenance of a registry of births.

City Inspector Griscom in 1842 gives a review of the sanitary condition of the city, together with many excellent recommendations. He demands that all certificates of death give data concerning the occupation of the deceased, so that industrial health hazards may be discovered. Finally we find him suggesting the taking of regular meteorological observations and the careful keeping of weather records.

City Inspector Archer, 1845 and 1846, demands the establishment of municipal slaughter houses, and of a hospital for pestilential and epidemic diseases. He succeeds in the enactment of a law requiring birth registration. Since it carried no penalty it proved ineffective.

City Inspector Downing (1852-1854 incl.) publishes excellent annual reports dealing with sanitary matters and vital statistics. He advocates the establishment of two bureaus, a Bureau of Sanitary Inspection and a Bureau of Registry and Statistics. The report for 1853 gives the text of an improved Birth, Marriage and Death Registration Act which Downing succeeded in having enacted.

City Inspector Delevan in his report for 1859 issues a blast at the street railway companies for the insanitary condition and overcrowding of the cars. In 1860 he urges the city to limit the number of persons living in a tenement room. Delevan appears to have been the first city inspector to advocate that a successful vaccination be required before

a child should be allowed to enter school.

It is apparent that these City Inspectors had an intelligent grasp of the health problems confronting the city, and it is likely that the chief fault was the failure of the Legislature to arm them with sufficient powers. I trust that future historians will erase the stigma placed upon these city officials by the report of the Citizens' Committee.

In an effort to correct the situation disclosed by the survey of the Citizens' Committee, health bills were repeatedly sent to the Legislature, only to be rejected because of the powerful influence of the City Inspector whose $1,000,000 was expended freely in the lobby at Albany. The Citizens' Committee thereupon enlisted the services of Mr. Dorman B. Eaton to draft suitable legislation to be presented to the state legislature. Mr. Eaton fortunately proved to be one of the few citizens who had kept pace with the progress of sanitary reforms in England and entered fully into the spirit of the great movement that for a quarter of a century had agitated the people of that country.

When the draft of the legislation came from the hands of Mr. Eaton it was evident that he had made a thorough study of the English health code. It provided for a Board of Health armed with extraordinary powers. According to Mr. Eaton a board of health should make its own laws, and sit in judgement on its own acts. He believed, however, that no legislature would pass a bill containing such powers if these powers were made a prominent feature of the Bill. For that reason he had adopted that involved expression peculiar to English law which required a judicial interpretation to determine the precise meaning.

Presented to the Legislature of 1865 the bill finally failed of passage. Thereupon the Citizens' Committee inaugurated a campaign to defeat for re-election those legislators who had voted against the bill. In this the *New York Times* rendered great service. Seventeen former members of the legislature failed to be renominated. In the new legislature the bill promptly passed both houses early in the session of 1866, and in March the Metropolitan Board of Health was organized.

I have dwelt with some detail on Eaton's work because its influence has not been sufficiently recognized by our medical historians. Garrison,[6] for example in speaking of the public health movement in those days says: "In the United States, the leading prime movers of public hygiene were Lemuel Shattuck, of Boston, who by his famous report to the Massachusetts Sanitary Commission (1850) did for New England what

Chadwick, Farr and Simon had done for England; John Shaw Billings, who strove to give their ideas a nation-wide application, while Stephen Smith, Hermann M. Biggs, William H. Park in New York, Baker in Michigan, Dixon in Pennsylvania, Welch and Fulton in Maryland, Fólsom and Sedgwick in Massachusetts, Joseph Jones in Louisiana, Winslow in Connecticut and Kober in the District of Columbia did yeoman service for their several states." Not even a mention here of Eaton.

You may be interested in an excerpt from a letter written to me in 1930 by our beloved "Popsy Welch." [7] "Lemuel Shattuck," he writes, "is called by Whipple, Winslow, Newsholme and others, the Edwin Chadwick of America, and perhaps in a sense he is, but his remarkable writings were without perceptible influence at the time, were based largely on Chadwick and other writers, and, above all were not associated with any such overwhelming presentation of facts as in the case of Chadwick. Dorman B. Eaton is more deservedly the Chadwick of America if achievement and influence as well as literary production be considered."

When the Metropolitan Board of Health was established in 1866 the Act provided for two bureaus, one the bureau of vital statistics, the other the sanitary bureau. All the activities of the new Department of Health, excepting only those dealing with the registration, tabulation and analysis of the records of births, deaths and marriages, were carried on by the sanitary bureau, whose field staff, the sanitary inspectors, were all physicians on part time service. They supervised isolation and quarantine, investigated cases of contagious diseases, performed vaccinations, made sanitary inspections to detect nuisances, etc. The reports of the Health Department of those days devote much attention to environmental sanitation,[8,9] to housing, offensive trades, removal of night soil, sewerage and plumbing. As director of the Department's chemical laboratory, Prof. Charles F. Chandler did outstanding work in detecting the adulteration of milk and other foods. Elisha Harris, as Registrar, introduced order into the mortality statistics, calling special attention to the frightful ravages of cholera infantum.

1875-1900

We come now to the most interesting era in the public health history of the city, the fourth quarter of the nineteenth century, for it was during this period that Pasteur, Koch and their pupils showed that

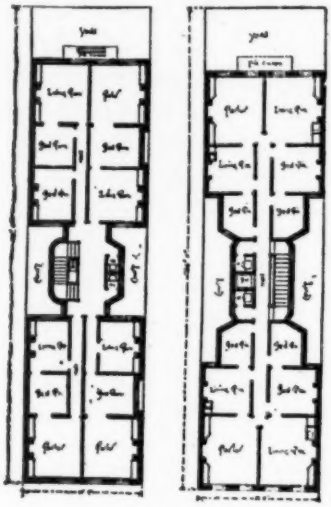

Fig. 5—One of the worst types of tenements, still in existence, in the so-called "dumb-bell" plan. Note that in 1879 this was awarded a prize. There are four families on a floor. Bedrooms receive light and ventilation only from a narrow shaft between the buildings.

a large number of diseases were caused by specific microörganisms. The earliest practical application of this new knowledge was made by Lister, in the field of surgery. Next, and of equal importance was its application in the field of sanitation and preventive medicine, and here the undisputed leader was Hermann M. Biggs.[10] In 1885 he had been made instructor in bacteriology in the Bellevue Medical College, the course being given in the then new Carnegie Laboratory in East 26th Street. The laboratory was officially directed by Janeway and Dennis, but actually Biggs did the work. In October 1887 the steamship "Brittania" had arrived at the New York Quarantine Station from Marseilles and Naples with a history of three deaths among the steerage passengers. Two more passengers died while the ship lay at quarantine, and from one of these cases, suspected to have been cholera, culture tubes inoculated from the intestinal contents were brought to the laboratory.

The examination by three independent observers, Prudden, Biggs and Weeks, showed that the disease was true cholera. All the immigrants

were then removed from the vessel, and several days later a number of other cases of cholera occurred among them. At this time Biggs had served with Janeway and others as a member of a conference committee between the Department of Health and The New York Academy of Medicine, created primarily to discuss the cholera situation. In 1888 Janeway, Prudden, Biggs and H. P. Loomis were appointed Consulting Pathologists to the Department of Health.

On several occasions Biggs suggested to Joseph D. Bryant, who was a power in the Board of Health, the creation of a Division of Pathology, Bacteriology and Disinfection, and funds for such a division were inserted in several of the budget requests, but were denied. Then, in August, 1892, when the city was in a panic because of the arrival at New York of several cholera-laden ships from Hamburg, the Board of Health secured an emergency appropriation for the establishment of a bacteriological laboratory to diagnose cholera. Dr. Biggs was placed in charge and given the title "Chief of the Division of Pathology, Bacteriology and Disinfection."

Similar emergency laboratories had been set up about that time in Hamburg, Bremen, Berlin and London, so that there was apparently nothing remarkable about New York City's action. Nevertheless it was an epoch making event, for whereas the several European laboratories were discontinued after the cholera emergency had passed, the laboratory established by the New York City Board of Health was continued as an integral part of the Health Department's services to practicing physicians. In fact, on the day the laboratory was opened, September 1, 1892, Biggs announced that it would be able to help physicians in the differential diagnosis of obscure cases; such as diphtheria and follicular tonsillitis. He also mentioned its value in the bacteriological examination of drinking water, milk and other foods, and spoke of bacteriologic research.

Biggs lost no time in carrying this program into effect. In April 1893 he brought Dr. William H. Park into the laboratory and assigned to him the problem of working out a practicable method of aiding physicians in the diagnosis of diphtheria. Within a short time Park had devised the diagnostic outfits for making throat cultures, and then the laboratory inaugurated the plan of having supplies of these diagnostic outfits available to physicians in conveniently located drug stores. Throat cultures left by the physicians at these drug stores stations

were collected daily by a messenger from the laboratory. After incubation overnight, they were examined early in the next day and the result telephoned to the attending physician. In January 1894 the laboratory offered to examine sputum for tubercle bacilli, and made suitable sputum bottles available at the drug store stations. Soon after, the laboratory offered to examine pus smears for gonococci and blood smears for malaria, also specimens of blood for the Widal reaction for the diagnosis of typhoid fever.

How marked the influence of the first bacteriologic diagnostic laboratory was on public health methods throughout the United States is well indicated by the following sentence taken from the preface of the first edition of Park's *Bacteriology in Medicine and Surgery*[11] published in 1899:

"The methods used in the laboratory for the isolation and identification of the typhoid, tubercle, and diphtheria bacilli have been given with special fulness, as the bacteriological examinations of the discharges of persons suspected to have typhoid fever, tuberculosis, or diphtheria are now generally made for those bacteria in the laboratories of the health departments of even the smaller cities, because of the manifest importance to the public of knowing where such sources of infection exist."

That is to say, within less than seven years the health departments of even the smaller cities were using the new tool conceived by Biggs when he opened the emergency cholera laboratory in 1892! The same opportunity was presented to the European cities mentioned above, but only Biggs had the vision to grasp it.

A valuable collateral service which can be rendered by the diagnostic laboratory of a health department, a service clearly recognized and promptly made use of by Biggs, is the securing of notification of disease. Two instances will suffice to show how effectively this was utilized. In the face of much opposition Biggs in 1894 had prevailed upon the Board of Health to make tuberculosis reportable. Hospitals and other institutions were ordered to report all cases, while private physicians were requested to do so. At the same time the diagnostic laboratory offered to make examinations of sputum for tubercle bacilli. This diagnostic aid was appreciated by physicians and the specimens submitted soon made up a substantial proportion of the cases of tuberculosis reported to the Health Department. In similar fashion eighteen years later,

in 1912, Biggs overcame the violent opposition to the reporting of venereal diseases. In that instance the laboratory announced that it would make Wassermann blood tests free of charge, a startling offer at that time for private laboratories were charging five or ten dollars for such tests.

In 1893, the year that Park had begun to work on diphtheria in the Health Department's laboratory, Behring announced the discovery of diphtheria antitoxin. At an international medical congress held in Budapest in 1894, several outstanding pediatrists were able to report their clinical experiences with this new therapeutic agent. Biggs, who attended the congress, was so impressed that he cabled Park to immunize horses and start making diphtheria antitoxin. So it came that the laboratory established less than two years before, embarked on a large additional field of activity, while still expanding the diagnostic service.

The diphtheria antitoxin produced by Park proved much more potent than any produced by Behring in Berlin or by Roux in Paris. Within a short time the laboratory received urgent pleas from the health departments of other American cities that they be permitted to purchase Park's product. Here, once again, Biggs showed his genius. Since there was no authority for permitting the city to go into serum production as a business, he secured the passage of an act by the State Legislature (1895), authorizing the New York City Department of Health to undertake the manufacture of serums and vaccines for the people of the city, and to sell any surplus products. The money derived from such sale was to be deposited in a special account known as "The Antitoxin Fund" and to be at the disposal of the Board of Health for research studies on serums and vaccines. For many years Park and his associates were kept busy manufacturing "surplus" products for sale to other cities; and the income thus obtained quickly enabled the laboratory to become one of the world's foremost research laboratories in the field of public health.[12]

Although officially only director of the Division of Pathology, Bacteriology and Disinfection, and a subordinate of the Sanitary Superintendent, Biggs since his appointment to this position in 1892, was a real power in the Health Department. In 1894 he inaugurated the pioneer campaign for the administrative control of tuberculosis, and gradually organized a program which was subsequently followed by health authorities throughout the world. In 1896 he was influential in having the

Board of Health adopt a section of the sanitary code prohibiting the sale of milk in the City of New York except under a permit and subject to the rules and regulations of said board. This may be said to mark the beginning of the modern effective system of controlling the quality of its milk supply. In 1897 Biggs was instrumental in inaugurating a system of school medical inspection, 150 part-time medical inspectors being added to the Health Department's staff for this purpose. In that year, also, the reporting of tuberculosis was made compulsory, even for private physicians. The formation of Greater New York in 1898 brings to a close this account of health activities during the fourth quarter of the nineteenth century.

Since 1900

The election in 1901 brought a reform administration into power with Seth Low as Mayor. The new mayor asked Biggs to accept appointment as Commissioner of Health, but Biggs feeling that he could not undertake the responsibilities of full administrative authority declined. He accepted, instead, appointment as the "General Medical Officer," a position which was largely free from administrative detail but which involved the development of all the broader policies of the Department. In this capacity he served for twelve years, under Lederle, under Darlington and under Lederle again, always behind the scenes as the real directive force, formulating and guiding the work of the Health Department. In fact as we look back to Biggs' association with the Department from 1892 to 1914 we realize that it was the golden era in the public health history of the city.

In 1902 as a result of experimental studies made by Miss Lillian Wald, a staff of seventeen municipal school nurses was established, the first to be employed in the United States. In 1903 the first tuberculosis nurses were appointed.

During 1903-4 a study by Park and Holt showed conclusively that there was no specific germ of "cholera infantum" and that summer diarrhea of infants was principally due to an excessive number of ordinary dirt bacteria in milk fed to infants.

In 1904 a commission appointed by the Board of Health for the study of respiratory diseases inaugurated the first attempt to deal effectively with pneumonia.

In the winter of 1904-5 a severe epidemic of meningitis resulted in

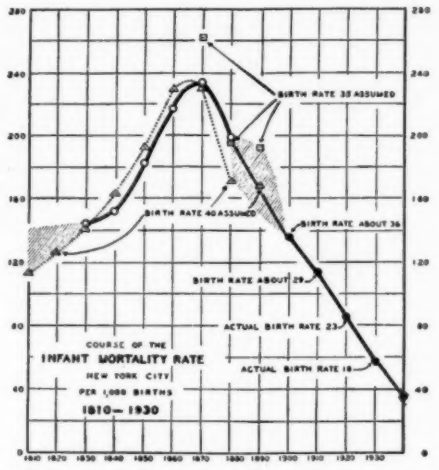

Fig. 6—Infant mortality in New York City 1910-1940. The rates are per 1000 live births. Small circles indicate the rate based on estimates of births arrived at from the census population under five.

important contributions to our knowledge of that disease.

In 1905 the Department of Health inaugurated the routine examination of school children for physical defects. In that year, also, on the recommendation by Dr. Doty, health officer of the port, extensive drainage work was begun on the marsh lands of Staten Island for the elimination of mosquitoes.

In 1906 country inspection of the city's milk supply was begun. The Board of Health also amended the sanitary code so as to class as adulterated, milk which was kept at a temperature above 50°F. Two years later milk was also defined as adulterated if it contained an excessive number of bacteria.[13] In 1906 the first municipal tuberculosis sanatorium was established by the Health Department at Otisville.

In 1907 an extensive outbreak of typhoid fever, traced to pollution of the Croton water led to a thorough survey of health conditions in the watershed, and disclosed serious defects in state health administration. This year saw also the registration of the first carrier, "Typhoid Mary," and her forcible detention by the Board of Health as a menace to the public health.

In 1908 the first division of child hygiene was established, Dr. S.

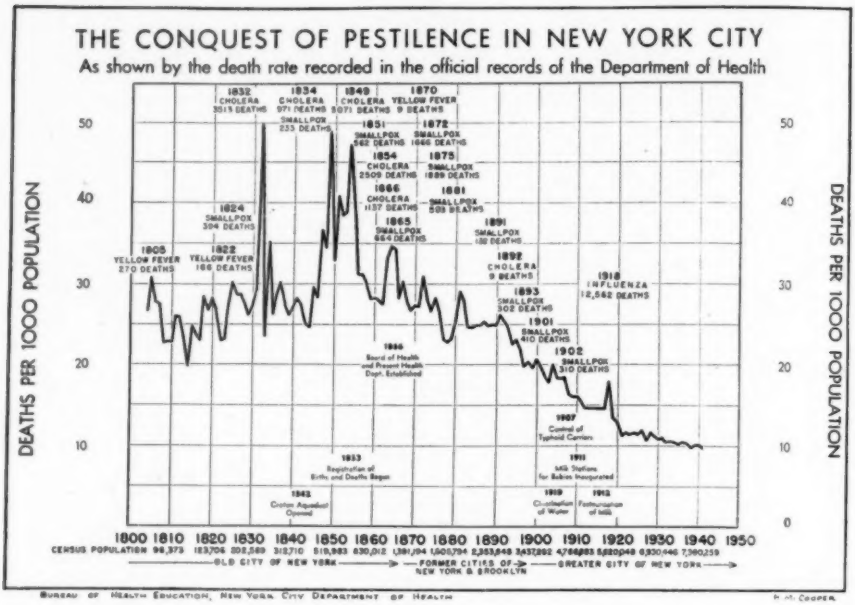
THE CONQUEST OF PESTILENCE IN NEW YORK CITY
As shown by the death rate recorded in the official records of the Department of Health
DEATHS PER 1000 POPULATION
DEATHS PER 1000 POPULATION
1800 1810 1820 1830 1840 1850 1860 1870 1880 1890 1900 1910 1920 1930 1940 1950
OLD CITY OF NEW YORK
FORMER CITIES OF NEW YORK & BROOKLYN
GREATER CITY OF NEW YORK
1805 YELLOW FEVER 270 DEATHS
1822 YELLOW FEVER 186 DEATHS
1832 CHOLERA 3515 DEATHS
1834 CHOLERA 971 DEATHS
1849 CHOLERA 5071 DEATHS
1870 YELLOW FEVER 9 DEATHS
1918 INFLUENZA 12,562 DEATHS
1842 Croton Aqueduct Opened
1866 Board of Health and Present Health Dept. Established
1893 Registration of Births and Deaths Began
1907 Control of Typhoid Carriers
1911 Milk Stations for Babies Inaugurated
1909 Chlorination of Water
1913 Pasteurization of Milk
Bureau of Health Education, New York City Department of Health
H. M. Cooper

Fig. 7—Course of New York City's general death rate 1804-1940.It is probable that the rates during the first half of the past century were somewhat higher than indicated, because of incomplete reporting.

Josephine Baker being placed in charge.[14]

In 1911 the first fifteen baby health stations were established. In 1912 forty more were added.

In 1911 the Board of Health introduced the grading of the milk supply, a system which remained in force until 1941. Pasteurization of all milk was enacted in 1913.

In 1912 the Health Department was reorganized into eight distinct bureaus, a ninth, the Bureau of Health Education being added in 1914. In that year, also, Biggs drew attention to the diseases of later life as a problem demanding the attention of health administrators, and had your speaker collect statistical data pertaining to this subject.[15]

Early in December 1913 Biggs resigned as General Medical Officer and on January 1, 1914, was appointed State Commissioner of Health. Under the new city Commissioner of Health, Dr. S. S. Goldwater, the position of General Medical Officer was abolished.

Goldwater's administration (January 1, 1914 to November 1, 1915) marks the first attempt at organizing health administration on a district basis, an experimental district health center being established in December 1914.[16] Subsequently, under Goldwater's successor Haven Emerson, several additional experimental health centers were established. All of them were, however, disbanded after the change of administration in 1918.

Other outstanding features of Goldwater's administration were:

The creation of a Division of Statistical Research, of a Division of Industrial Hygiene, and of a Bureau of Health Education.

A tabulation and analysis of vital statistics by sanitary areas made by Guilfoy and Wynne.

Provision for the annual physical examination of foodhandlers.

Under the administration of Commissioner Haven Emerson (from late in 1915 to 1918), the World War placed considerable burdens on the Department of Health, depleting its medical and nursing staff and making extraordinary demands on the laboratory in order to supply the army with serums and vaccines.

In 1916 the city experienced the most extensive and most serious epidemic of poliomyelitis ever recorded, either before or since.

The same is true of the pandemic of influenza beginning in the fall of 1918.

Under the administration of Commissioner Copeland and his successor Commissioner Monaghan, Dr. Wynne in coöperation with Dr. Arthur W. Bingham, President of the Medical Board of the Willard Parker Hospital, effected a thorough reorganization of the Health Department's contagious disease hospitals, introducing the cubicle system, aseptic nursing and other important reforms. Dr. Wynne remained in charge of this hospital service until his appointment as Commissioner of Health in 1928.

Mention should also be made of the remarkably effective campaign carried on against diphtheria under the leadership of Commissioner Shirley W. Wynne. During the year immediately before this campaign began there were 642 deaths from diphtheria. Last year, in 1941, there were only 10!

Under Dr. Wynne there were also begun tuberculosis case-finding by means of extensive chest x-ray surveys, and the consultation service for suspected cases of tuberculosis under the care of private physicians,

and for suspected cases of venereal disease.

Finally it was Dr. Wynne who initiated the present program of District Health Administration which has been so extensively developed by Commissioner Rice under Mayor La Guardia's administration.

Before closing this retrospect I should like to mention the invaluable aid extended to the Department of Health by The New York Academy of Medicine almost since its organization in 1847. I referred to such help in speaking of the beginnings of the campaign to provide pure milk for the people of this city. Ever since then, but particularly since the formation of the Academy's Committee on Public Health in 1911, the Department has had invaluable assistance in its efforts to promote the public health. We are indeed very grateful.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETING

DECEMBER 3—*The New York Academy of of Medicine.* Executive session—Reading of the minutes. ¶ Papers of the evening, scientific program in cooperation with the Section of Genito-Urinary Surgery. Prostatic carcinoma—a] Diagnosis of prostatic carcinoma and its metastases, including value of phosphatase determinations, Charles B. Huggins, Professor of Surgery, University of Chicago; b] Treatment of prostatic carcinoma, Benjamin S. Barringer, Attending Surgeon, Department of Urology, Memorial Hospital. ¶ Report on election of Fellows. ¶ Report on election of Academy officers.

DECEMBER 17—*The Harvey Society in affiliation with The New York Academy of Medicine.* The Third Harvey Lecture, "Poliomyelitis," John R. Paul, Professor of Preventive Medicine, Yale University School of Medicine.

JANUARY 7—*Annual Meeting. The New York Academy of Medicine.* ¶ Executive session—a] Reading of the minutes; b] Presentation of Certificates of Fellowship. ¶ Presentation of Annual Reports (to be read by title), The Council, The Trustees, The Treasurer, Committees. ¶ Address of the retiring president—Malcolm Goodridge. ¶ Address of the incoming president—Arthur F. Chace. ¶ Paper of the evening—Scientific program in cooperation with the Section of Surgery, and the New York Surgical Society. Shock—a major war problem in medicine and surgery—Alfred Blalock, Professor of Surgery, Johns Hopkins University School of Medicine. ¶ Report on election of Fellows.

JANUARY 21—*The Harvey Society in affiliation with The New York Academy of Medicine.* The Fourth Harvey Lecture, "Studies on the Pathological Physiology of Cushing's Syndrome," Fuller Albright, Assistant Professor of Medicine, Harvard Medical School.

SECTION MEETINGS

DECEMBER 1—*Dermatology and Syphilology.* ¶ Presentation of cases—a] From The New York University College of Medicine; b] Miscellaneous cases. ¶ Discussion. ¶ Executive session.

DECEMBER 4—*Surgery.* ¶ Reading of the minutes. ¶ Case presentations—a] Cases illustrating the first paper of the evening, J. William Hinton. b] Stenosing ulcer of the duodenum with severe hemorrhage, treated by gastrojejunostomy, William A. Fraser. ¶ Papers of the evening—The intractable duodenal ulcer; evaluation of surgical procedures, J. William Hinton, discussion opened by Felix de Amesti, Santiago, Chile, Professor of Surgery, University of Santiago. b] Injuries to the larynx and trachea, Robert L. Nach (by invitation) and Milton Rothman. ¶ General discussion opened by Francis X. Timoney. ¶ Executive session.

DECEMBER 8—*Combined Meeting. New York*

Neurological Society and the Section of Neurology and Psychiatry. ¶ Papers of the evening—a] The use of focused ultra-sound waves for the production of transcranial focal brain lesions, John G. Lynn (by invitation), Tracy J. Putnam, discussion by Harold G. Wolff, Charles Davison; b]A psychiatric study of forty torpedoed seamen, Lawrence S. Kubie, Leo Stone (by invitation), Sydney Margoline (by invitation), Mark Kanzer (by invitation), discussion by Daniel Blain, Howard W. Potter; c] The role of instinct in human behavior, J. Marmor, discussion by Israel S. Wechsler, A. Kardiner.

DECEMBER 10—*Pediatrics.* ¶ Reading of the minutes. ¶ Presentation of cases—a] A case illustrating teaching of body mechanics, Miriam T. Sweeney (by invitation); b] A case of weak feet and poor posture, Beckett Howarth. ¶ Papers of the evening—Discussion of posture and training, William T. Green, Children's Hospital, Boston (by invitation), Beckett Howorth. ¶ General discussion.

DECEMBER 15—*Medicine.* ¶ Executive session —Reading of the minutes. ¶ Papers of the evening—Diseases of the liver and biliary system—a] Treatment of cirrhosis, Arthur J. Patek, Jr. (by invitation); b] Eleven years' experience with thorotrast hepatospienography, Wallace M. Yater (by invitation); c] The conservative treatment of gallbladder and biliary tract disease, Carl H. Greene, discussion by Franklin M. Hanger, Reuben Ottenberg, Leopold Lichtwitz.

DECEMBER 16—*Otolaryngology.* ¶ Reading of the minutes. ¶ Paper of the evening—Tumors of the nasal sinuses, LeRoy A. Schall, Boston, Mass. (by invitation), discussion, John D. Kernan, Maurice Lenz, Hayes Martin. ¶ General discussion. ¶ Executive session.

Genito-Urinary Surgery—The Section of Genito-Urinary Surgery did not hold its regular meeting on December 16, as it combined its scientific program with that of the Stated Meeting on December 3.

DECEMBER 18—*Orthopedic Surgery.* ¶ Reading of the minutes. ¶ Papers of the evening—a] Plastic surgery in orthopedic cases, Yolande H. Huber, discussion by Leo Mayer; b] Massive skin plastics for release of orthopedic deformities, David M. Bosworth, discussion by Joseph B. L'Episcopo; c] Skin grafting of war wounds, John M. Converse (by invitation). ¶ General discussion. ¶ Executive session.

DECEMBER 21—*Ophthalmology.* ¶ Instruction hour 7:30 to 8:00 o'clock, moving picture and exhibit, Henry Minsky. ¶ Executive session—Reading of the minutes. ¶ In memoriam—Samuel P. Oast, by Clyde McDannald. ¶ Papers of the evening—Pathology of unsuccessful operations for cataract, Theodore L. Terry (by invitation), discussion by John M. McLæan. ¶ New instruments, apparatus —New atraumatic catgut suture for use in cataract surgery, Wendell Hughes, Experimental studies—Hunter Romaine (by invitation), discussion by Loren P. Guy. ¶ Presentation of cases—a] Tuberous sclerosis, Elizabeth F. Constantine (by invitation), discussion by Thomas I. Hoen; b] Cyst of the iris, Herbert Katzin (by invitation), discussion by Kaufman Schlivek.

DECEMBER 22—*Obstetrics and Gynecology.* ¶ Executive session—Reading of the minutes. ¶ Case reports—Ruptured uterus—an account of recent cases and brief review of cases for the past ten years at the New York Lying-In Hospital, Earl B. King (by invitation). ¶ Papers of the evening—a]Evaluation of the pregnandiol complex as an index of ovarian and uterine function, determined by the Venning-Browne test, Samuel L. Siegler; b] The effect of mixed conjugated estrogens from pregnant mares' urine (premarin) in the treatment of menopause, Theodore Neustaedter. ¶ General discussion.

JANUARY 5—*Dermatology and Syphilology.* ¶ Presentation of cases—a] From Vanderbilt Clinic and Presbyterian Hospital, College of Physicians and Surgeons. b] Miscellaneous cases. ¶ Discussion. ¶ Executive session.

JANUARY 12—*Neurology and Psychiatry.* ¶ Papers of the evening—a] The endocrine dysergias and anergias, Otto Marburg (by invitation), discussion by Bernard Sachs, Tracy J. Putnam; b] Sex and chemistry of the brain, Arthur Weil, discussion by Harry Sobotka, Richard J. Block (by invitation); c] War neurosis, John Frosch (by invitation), discussion by Sandor Rado, A. Kardiner. ¶ Executive session.

JANUARY 13—*Historical and Cultural Medicine.* ¶ Executive session—Appointment of nominating committee. ¶ Papers of the evening—Vesalius Celebration, honoring the Quadricentenary of the publication of De Humani Corporis Fabrica (1543)—a] "Andreas Vesalius, Professor in The Medical School in Padua,' Arturo Castiglioni (by invitation); b] "The Position of Vesalius in The History of Medicine," Henry E. Sigerist (by invitation), discussion by James F. McDonald, Gregory Zilboorg, Mr. William M. Ivins, Jr. (by invitation). ¶ Exhibit of books of Andreas Vesalius, from the library of the Academy.

JANUARY 14—*Pediatrics.* ¶ Reading of the minutes. ¶ Papers of the evening—a] A simplified method of making infant formulae, Katharine K. Merritt, Irene Waters, A.B. (by invitation), Emma Mike, B.S. (by invitation), discussion by Donovan J. McCune; b] The initial nasopharyngeal flora of infants in relation to ultra violet radiation, J. C. Torrey (by invitation), Martha Reese (by invitation), discussion by Samuel Z. Levine; c]New problems in the treatment of pneumonia, Rosa Lee Nemir (by invitation), discussion by Jesse G. M. Bullowa (read by Gertrude Weiss), Wheelan D. Sutliff (by invitation).

JANUARY 18—*Ophthalmology.* ¶ Instruction hour 7:00 to 8:15 o'clock; motion pictures—surgical operations on the eyes, Institute of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, New York Eye & Ear Infirmary. ¶ Executive session—Reading of the minutes. ¶ Papers of the evening—a] Military ophthalmology, William Thornwall Davis (by invitation); b] Penicillin and sulfadiazine treatment of experimental intraocular infection with pneumococcus, Ludwig Sallmann (by invitation), discussion by Karl Meyer (by invitation); c] The topography of the orbit with particular reference to retrobulbar injection, Robert Lambert, Virginia Lubkin (by invitation). ¶ Presentation of cases—a] Harada's disease (?) —report of a case, I. Givner, discussion by Ludwig Sallmann (by invitation).

Orthopedic Surgery. Due to the annual meeting of the American Academy of Orthopedic Surgeons in Chicago on January 15, the regular meeting of the Section was not held.

JANUARY 20—*Genito-Urinary Surgery.* ¶ Reading of the minutes. ¶ Case reports—a] Rectourethral fistula with perirectal abscess, C. V. Burt (by invitation); b] Embryonic polycystic kidney with autopsy findings, Vincent Corrigan (by invitation); c] Fused unascended kidneys with changes in pregnancy, Simon A. Beisler; d] Polycystic kidneys, Ralph C. Yeaw (by invitation). ¶ Paper of the evening—Spot test for rapid analysis of calculi, Julius H. Winer, Lt., M.C., A.U.S. (by invitation), M. R. Mattice. ¶ General discussion. ¶ Executive session.

JANUARY 20—*Otolaryngology.* ¶ Reading of the minutes. ¶ Papers of the evening—a] Pathology of petrositis, report of three cases with lantern slide demonstration, Andrew A. Eggston, discussion by Wesley C. Bowers, John R. Page, Dorothy Wolff, St. Louis, Mo. (by invitation); b] Surgical treatment of carcinoma of

the larynx, presentation of cases, moving picture, Maxwell Ryan (by invitation). ¶ General discussion. ¶ Executive session.

JANUARY 21—*Joint Scientific Session. Medicine and the New York Heart Association, Heart Committee of the New York Tuberculosis and Health Association.* ¶ Annual report of the New York Heart Association, Edwin P. Maynard, Jr. ¶ Papers of the evening—a] Cardiac problems in wartime, Paul D. White (by invitation), Physician, Massachusetts General Hospital, Lecturer in Medicine; b] Vascular and neurological lesions of the extremities in survivors of shipwreck, James C. White, Commander (MC) U.S.N.R., Neurosurgical Service, U. S. Naval Hospital, Chelsea, Mass. and Massachusetts General Hospital; c] Experiences with various cardiac problems in the present war, Arthur M. Master, Commander (MC) U.S.N.R., Cardiologist, National Naval Medical Center, Bethesda, Maryland.

JANUARY 26—*Section of Obstetrics and Gynecology.* ¶ Executive session — reading of the minutes. ¶ Case reports—Failure of corpus luteum medication in an Rh negative patient having two consecutive miscarriages—Robert S. Millen. ¶ Papers of the evening—a] Study of edema and toxemia of late pregnancy in relation to sodium and potassium imbalance—Thomas J. Parks (by invitation); b] Treatment for delayed menstruation combined with a test for early pregnancy, Haig Carpatyan (by invitation). ¶ General discussion.

AFFILIATED SOCIETIES

DECEMBER 10—*New York Pathological Society in affiliation with The New York Academy of Medicine.* ¶ Paper of the evening—The chronology of mammary cancer, James Ewing. ¶ Executive session.

DECEMBER 21—*New York Roentgen Society in affiliation with The New York Academy of Medicine.* ¶ Papers of the evening—a] The influence of hormonal changes on carcinoma metastases to bone, Helen Q. Woodard (by invitation), discussion by Alfred Hocker (by invitation); b] Radioactive isotopes in the determination of circulating erythrocyte volume, Robert Anderson (by invitation), discussion by Lloyd Craver (by invitation); c] Dosage calculations for various combinations of parametrial needles with intracervical tandems, James Nolan (by invitation), discussion, Gray Twombley (by invitation). ¶ Executive session.

JANUARY 18—*New York Roentgen Society in affiliation with The New York Academy of Medicine. Past presidents' program.* ¶ Papers of the evening—a] Two cases of ileocaecal carcinoma, Harry M. Imboden; b] A case of mediastinal tumor, presumably lymphosarcoma, Ross Golden; c] Two cases of uncommon chest lesions in newborn infants, Robert E. Pound; d] A non-traumatic diverticulum of the prostatic urethra, A. L. Loomis Bell. ¶ Discussion open to members. ¶ Executive session.

JANUARY 28—*New York Pathological Society in affiliation with The New York Academy of Medicine.* ¶ Presentation of cases—a] A case ot cystic fibrosis of the pancreas in an infant, Marcel Pahmer (by invitation); b] A case of generalized thromboangiitis, Thomas G. Morrione (by invitation). ¶ Papers of the evening—a] Concretions in the pituitary of the fetus and the newborn, Alfred Plaut; b] Diagnosis of chondrosarcoma of bone, Louis Lichtenstein, Henry L. Jaffee.

A COMMITTEE TO STUDY MEDICINE AND THE CHANGING ORDER has been organized by The New York Academy of Medicine. The objectives of this Committee are:

To be informed on the nature, quality and direction of the economic and social changes that are taking place now and that are clearly forecast for the immediate future; to define in particular how these changes are likely to affect medicine in its various aspects; to determine how the best elements in the science of medicine and its services to the public may be preserved and embodied in whatever changed social order may ultimately develop.

The Committee plans to survey the changes that are currently taking place in our economic and social organization and to consider also any changes which are likely to take place during the next decade.

In this survey the Committee will solicit information and opinion from a wide variety of groups, including sociologists, economists, representatives of organized labor, industrialists, bankers and politicians.

Also, in this connection, the Committee will solicit the coöperation of those intimately connected with medicine in the capacities of deans of medical schools, teachers of medicine, hospital authorities, hospital clinicians, public health workers, those interested in graduate education, physicians in industrial medicine, medical social workers, and workers in voluntary health organizations.

We wish to emphasize the point that the Committee will devote itself primarily to the study of how, within the changing social order, the best qualities in medical service, in medical education and in medical research can be preserved and developed.

It is expected that the study will continue until sufficient evidence has been accumulated to make possible a considered report.

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